Aggressive systemic mastocytosis mimicking sclerosing cholangitis

A 43 year-old woman presented with fever, abdominal pain, epato-splenomegaly, ascites, cholestasis, anemia, thrombocytopenia and previous diagnosis of sclerosing cholangitis based on liver biopsy and endoscopic retrograde cholangiopancreatography(ERCP). The bone marrow biopsy and the revision of liver biopsy using antitryptase stain diagnosed systemic mastocytosis. Because of the aggressive course of the disease the patient was treated with an acute myeloid leukaemia chemotherapy regimen without success.

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Mastocytosis is a heterogeneous group of disorders with accumulation and proliferation of mast cells in tissues.[1]

There is evidence of derivation of mast cell from hematopoietic progenitor cell and systemic mastocytosis can be considered a mieloproliferative disorder.[2-4]

The functional characteristics of mast cells and the various localizations of the disease are associated with a spectrum of clinical pictures that can mimic several diseases making the diagnosis difficult.

Systemic mastocytosis may show either an indolent or an aggressive clinical course.

In aggressive systemic mastocytosis the infiltration of mast cells causes impairment function of involved organs. The liver is frequently involved, but rare cases of biliar ducts infiltration have been previously described.

Treatment of aggressive systemic mastocytosis can be difficult and there is no standard therapy.[5]

We describe a case of aggressive systemic mastocytosis which presented with a clinical picture simulating sclerosing cholangitis treated unsuccessfully with polychemotherapy.

Case Report

A 43-year-old woman was admitted to hospital in February 2002 because of abdominal pain, diarrhoea, fever, recurrent episodes of flushing, sweating and weight loss. She denied any use of medication, drug and alcohol abuse, blood transfusion. Physical examination revealed mild hepatomegaly, important splenomegaly, ascites and bilateral pleural effusion. There were no skin lesions, lymphadenopathy or signs of chronic liver disease. Laboratory examination at the time of admission showed a white blood cell count of 4,600/mm^3 with a normal differential count, hemoglobin 8,8 g/dL, platelet count 130000/mm^3. The total serum bilirubin level was 1.0 mg/dL (normal 0.2-1.0), alkaline phosphatase level was 640 U/L (normal 47-125), gamma-glutamyltransferase level was 201 U/L (normal 7-50), total serum protein 6,0 g/dl (normal 6.2-8.0) albumin 2.5 g/dL (normal 3,5-5,0), sedimentation rate was 40 (normal <25), PC-reactive level was 58 mg/L (normal <5) the prothrombin time was 60% (normal 70-130), the partial thromboplastin time was 31,8 (normal 23-38), fibrinogen was 307 mg/L (normal 150-450). Aspartate aminotransferase, alanine aminotransferase, amylase and creatinine levels were normal. Serological testing for hepatitis A, B and C, HIV, cytomegalovirus, rickettsia, leishmania, mycobacterium tuberculosis, malaria, salmonella and brucella was negative. Autoimmune and tumoural markers, and blood and faecal cultures were negative. A computed tomography (CT) scan showed apical small nodule in the right lung, bilateral pleural effusion, mild hepatomegaly, splenomegaly with signs of portal hypertension, enlarged lymph nodes, 2 cm in diameter, near the liver. The gastro- and colonoscopy were negative. The bone marrow biopsy showed hypercellularity with hyperplasia of myeloid cells and diffuse and nodular infiltration of monocytes. Reticular fibres were increased. The diagnostic paracentesis yielded ascitic fluid of transudative origin; bacterial cultures were negative. ERCP showed reduced biliar ducts. Percutaneous liver biopsy diagnosed primitive sclerosing cholangitis at the II stage with fibrosis and periportal flogosis and piecemeal necrosis of biliar type. The patient was treated with steroids with improvement of her general condition, disappearance of fever and decrease of hepatic stasis index. She was discharged on March 25, 2002. One month later during tapering of steroids the patient was admitted to hospital again with fever, diarrhoea and ascites. White blood cell count was 6,900/mm^3 with a normal differential count, hemoglobin 8,5 g/dL, platelet count 47000/mm^3. The total serum bilirubin level was 4.0 mg/dl (normal 0.2-1.0), alkaline phosphatase level was 688 U/L (normal 47-125), gamma-glutamyltransferase level was 218 U/L (normal 7-50), total serum protein 7,7 g/dl (normal 6.2-8.0) albumin 2.4 g/L (normal3,5-5,0), the prothrombin time was 53% (normal 70-130), the partial thromboplastin time was 49,8 (normal 23-38). Aspartate aminotransferase, alanine aminotransferase, amylase and creatinine levels were normal. Abdomen CT scan and ultrasound-doppler showed occlusion of the sovrahepatic veins and diagnosis of Budd-Chiari syndrome was made. Steroids were increased without improvement.

The patient was first seen in our hospital on May 14, 2002 for suspected lymphoma. She presented fever, flushing, gastric pain, episodic and colicky abdominal pain, scleral jaundice, ascites, edema of lower limbs, hepatomegaly (6 cm below the right costal margin) and splenomegaly (8 cm below the left costal margin). Blood tests showed white blood cell count of 3.000/mm^3 with normal differential count, hemoglobin 8.8 g/dl, platelet count of 33.000/mm^3, total serum bilirubine 2.73 mg/dL, conjugated bilirubune 1.22 mg/dL, alkaline phosphatase 1435 U/L with increased hepatic isoenzyme, gamma-glutamyltransferase 202 U/L, total serum protein 7.7 g/lL(normal 6.4-8.0) albumin 2.9 g/dL, policlonal hypergammaglobulinemia, IgG 2.130 mg/dl (normal 680-1.445), IgA 167 mg/dL (normal 70-373), IgM 345 mg/dlL(normal 40-248), lactate dehydrogenase level 393 U/L (normal 10-500), ammonia 250 ug/dL (normal 40-80), sedimentation rate 98, $\beta_2$microglobuline 4.41 ug/mL (normal 0.6-2.6), prothrombin time 68% and partial thromboplastin time 39 sec, antithrombin 61% (normal 80-130), fibrinogen 348 (normal 250-450), tryptase > 200 ng/ml. The transaminases, creatinine, glycemia levels and urinalysis were normal. All microbiologic and viral serology and blood cultures were repeated and resulted negative. The autoimmune markers were positive for antineutrophil cytoplasmic antibodies (title 52.7 EU/mL), for Coombs test anti-IgG, cryoglobulins (monoclonal IgM and polyclonal IgG with cryocrite 0.9%), cryoagglutinine (title 1:128) and for anti-platelets antibodies (anti glicoprotein IIbIIIa, IbIX and IaIIa); antinuclear antibodies, anti-smooth-muscle antibodies, antimitochondrial antibodies were negative. A chest and abdomen CT scan showed multiple lung nodules, severe splenomegaly with multiple nodules and hepatomegaly without focal damage and thinning of sovrahepatic and hepatic cava veins.

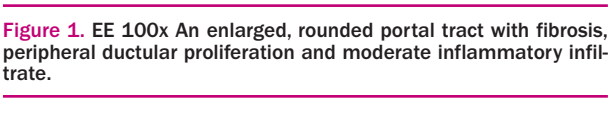

Figure 1. EE 100x An enlarged, rounded portal tract with fibrosis, peripheral ductular proliferation and moderate inflammatory infiltrate.

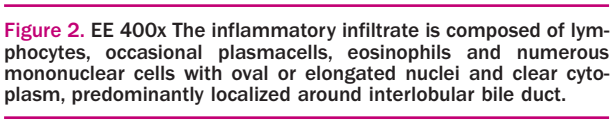

Figure 2. EE 400x The inflammatory infiltrate is composed of lymphocytes, occasional plasmacells, eosinophils and numerous mononuclear cells with oval or elongated nuclei and clear cytoplasm, predominantly localized around interlobular bile duct.

Skeletal X-ray revealed multiple osteolytic areas in skull, ribs, thigh-bones, shoulders and pelvis. Paracentesis showed ascites containing total protein level of 2.94 g/dL with negative bacterial cultures. Bone marrow biopsy showed massive multifocal infiltration (>50%) of spindle-shaped cells with sometimes only a few metachromatic granules in a pale cytoplasm and oval nuclei. Using antitryptase immunoperoxidase stain these cells were identified as atypical mast-cells. There was fibrosis and hyperplasia of residual hemopoietic cell series.

Flow cytometric immunophenotypic studies of bone marrow aspiration revealed a population of large size cells compatible with mast cells (CD45+, CD117+, CD33+, CD16±, CD11B±, CD34-, CD14-). Cytogenetic studies of the bone marrow yielded a normal karyotype.

The mutation Asp to Val at codon 816 in the c-kit gene was demonstrated in the mast cells of bone marrow. Liver biopsy previously carried out was reviewed using antitryptase immunoperoxidase stain and showed dense periportal infiltrate of mast cells with the same characteristics as the ones in bone marrow. These cells sometimes have periductal localizations with necrosis of adjacent hepatocytes; there was generative bile ductules and fibrosis.

On May 25, 2002 the patient received a course of chemotherapy with idarubicin at a dose of 12 mg/m^2 for two days and cytarabine at a dose of 100 mg/m^2 by continuous infusion for five days. During chemotherapy the patient was treated with histamine H1 and H2 antagonists and prednisone at a dose of 0,5 mg/kg. Chemotherapy was well tolerated and bilirubin, alkaline phosphatase and gamma-glutamyltransferase levels started decreasing, fever disappeared and hepatosplenomegaly was reduced. In June, 2002, during neutropenia post-chemotherapy, fever started again and the patient developed bilateral multiple pulmonary infiltrates treated with broad spectrum antibiotics and amphotericin B without resolution. A bronchioalveolar lavage was performed identifying a population of cells CD117+, CD11B+, CD33+, CD25+, compatible with mast cells. Blood cultures were repeatedly negative. On June 11 2002, the general condition of the patient worsened and she went into a coma. A cranial CT scan without contrast carried out in the first 24 hours was negative. The hepatic function progressively worsened and the patient developed haemorragic syndrome even with multiple platelet transfusions. The prothrombin time was 20% and the partial thromboplastin time was >120", antithrombin was 47%, fibrinogen 244 mg/dl platelet count was 7000/mm^3, white blood count was 4300/mm^3. She died on June 18, 2002. The autopsy revealed massive multifocal infiltration of atypical mast cells in the spleen, liver, bone marrow and lungs; there were diffuse dural petechiae and residual blood in stomach.

Discussion

In mastocytosis mast cells can accumulate and proliferate in many tissues.

The most frequent tissue involved is the skin, usually with pigmented maculopapular lesions (urticaria pigmentosa), but several organs can be involved: bone marrow, liver, spleen, lymph nodes, gastrointestinal tract, skeletal system, giving a broad spectrum of clinical manifestations.

When the disease is diffuse, bone marrow is almost always involved[6] and lack of skin lesions seems to relate to an aggressive course.[7]

The classification of these disorders was recently debated and in 2001 a new classification system was proposed subdividing mast cell disorders into cutaneous mastocytosis, that usually affects children, and systemic mastocytosis. The latter is further divided into indolent systemic mastocytosis, systemic mastocytosis with an associated clonal hematologic non mast cell lineage disease, aggressive systemic mastocytosis and mast cell leukaemia.[8]

While cutaneous mastocytosis is almost always a benign disease, above all when affecting children, systemic mastocytosis is considered a neoplastic disorder of multipotent hematopoietic stem cell.

The clonal nature of the disorder has recently been suggested by the demonstration in the mast cells of many cases of systemic mastocytosis of acquired point mutations in c-kit gene encoding the tyrosine kinase receptor for stem cell factor, a major cytochine involved in mast cell growth. The most frequent alteration found is the mutation Asp to Val at codon 816 (c-kit D816V) resulting in a constitutively activated stem cell factor receptor which stimulates mast cell growth and prevents apoptosis.[9] In some patients the same mutation has been detect-

Figure 3. EE 200x Bone marrow trephine biopsy shows paratrabecular infiltrate of elongated blunt-ended or spindle shaped mononuclear cells with pale to lightly eosinophilic cytoplasm. In the nodular lesion (on the right) there is a central focus of lymphocytes encircled by elongated or round cells with clear cytoplasm.

Figure 4. EE 400x The mononuclear spindle cells, morphologically similar to fibroblasts, are mastcells, marked by alkaline- phosphatase linked monoclonal antibody specific against human mast cells tryptase (Streptavidin-Alkaline Phosphatase Immunohistochemical method).

ed also in B cells and monocytes.[10]

Granules of mast cells contain many substances (histamine, leukotrienes, prostaglandins) that, when released, are responsible for various symptoms sometimes severe and life-threatening: pruritus, headache, syncope, flushing, hypotensive shock, diarrhoea, abdominal pain, anaphylaxis. Symptoms of the pathology are further related to the infiltration of the organs with or without loss of function. In aggressive systemic mastocytosis the clinical picture is charaterized by loss of function of involved organs: patients may have ascites, malabsorption, osteolysis, pancitopenia. Constitutional symptoms may be present with weight loss, fatigue, fever. Granules of mast cells contain heparin and coagulation disorders with bleeding tendency are described. Mast cells contain enzyme tryptase and elevated levels of this enzyme are detected in the blood of patients particularly in aggressive forms and correlate with the burden of the disease.

Morphological alterations of mast cells can be seen in systemic mastocytosis, particularly in the aggressive form: mast cells may be hypo-agranulated, immature, spindle-shaped, with eccentric oval nucleus, bilobed or multilobed nucleus. Diagnosis needs histological demonstration of infiltration of mast cells in tissues with appropriate stains: Giemsa, toluidine blue, chloroacetate esterasi and more recently with antitryptase stained tissue sections.[5,11] Antitryptase antibody is particularly sensitive also in cases with highly atypical mast cells with few metachromatic granules, that can be toluidine-blue or chloroacetate-esterase negative. Infiltration of neoplastic mast cells must be differenziated from reactive scattered infiltrate of typical round, metachromatic mast cells in other non mast cell disorders[12] The presence of dense infiltrate of atypical mast cells is the most important histological feature of mastocytosis.

In mastocytosis specific recurrent alterations of cell surface phenotype have been demonstrated. Mast cells in normal tissue express CD117 (c-Kit receptor) and CD33 but do not express CD25 and CD2. The two latter antigens are often expressed by mast cells in systemic mastocytosis and the detection of CD2 and/or CD25 on CD117+/CD34- mast cells is considered very sensitive and specific for mastocytosis.[13]

For the pleiomorfic presentation of the pathology, systemic mastocytosis may escape detection, above all in cases without skin involvement, unless special stains of tissue sections are used. In our patient the initial diagnosis of sclerosing cholangitis based on ERCP and liver biopsy was corrected using antitryptase stained tissue sections of liver and bone marrow.

Liver is frequently involved in systemic mastocytosis.[11,14-16] The reported alterations are hepatomegaly (mean frequency in the different series 48%), elevation of serum alkaline phosphatase and less often of aminotransaminases , portal hypertension, ascites, cirrhosis. In normal liver tissue mast cells are found in very low number. In systemic mastocytosis liver biopsies described in literature show inflammatory cellular infiltration with mast cells, dense mast cell patches, fibrosis and rarely cirrhosis. Mast cell infiltration is described mainly within the portal tracts.

In literature rare cases with involvement of biliar ducts system have been described.

Yam et al reported a diffuse mast cell infiltration of gall bladder in a patient with systemic mastocytosis at cholecystectomy.[16]

Baron et al reported a case of a woman with systemic mastocytosis with infiltration of biliar ducts revealed by ERCP and brush cytology.[17]

Kyriakou et al described four cases with labotatory findings compatible with autoimmune cholangitis and mast cell infiltration of bile ducts.[18]

Safyan et al reported a case of systemic mastocytosis associated with acute myeloid leukaemia with focal infiltration of ductal epithelium and patchy cholestasis.[19]

Up to the present there is no standard therapy for aggressive systemic mastocytosis.[5,20,21]

Mediator-related symptoms are treated with drugs that antagonize the effects of mediators or decrease mast cell degranulation: antihistamines 1 and 2, disodium cromoglycate, ketotifen, acetyl-salicylic acid, proton pump inhibitors. Some symptoms, like ascites and malabsorption, may improve with corticosteroids. Biphosphonates and radiotherapy have been reported to relieve pain of bone lesions or osteopenia.[18,22] Symptoms related to accumulation and infiltration of tissue with loss of function are difficult to treat because of poor sensibility of mast cells to radiotherapy and chemotherapy. Recently some

cases have been treated with interferon alpha with controversial results;[23-26] the efficacy of the drug appears rather low.[27] Tefferi et al reported a case of systemic mastocytosis treated with 2-chlorodeoxyadenosine with reduction of mast cell infiltration.[28] Chemotherapy has been used in aggressive systemic mastocytosis with poor response, but up to now limited published data have been available.[7]

Inhibition of activated c-kit receptors might be a new potential therapeutic approach. Currently available c-kit inhibitors like STI571 have been ineffective in suppressing proliferation *in vitro* of neoplastic mast cells with c-kit D816V mutation.[29,30] Recently indolinone derivatives have been tested. These compounds are able to inhibit in vitro phosphorylation of mutated c-kit receptors resulting effective in killing neoplastic mast cells.[31,32]

Resistance of neoplastic mast cells to chemotherapy has also been shown by poor response of mast cell leukemia to chemotherapy;[33-35] furthermore in a reported case of mastocytosis associated with hematological malignancies bone marrow allotransplantation was able to obtain remission of hematologic disease but there was persistence of mastocytosis.[36] Only one case of aggressive systemic mastocytosis which obtained remission with cycles containing daunorubicin and citarabine has been reported in literature; the patient was subsequently treated with bone marrow allotransplantation but relapsed after 4 months and died with massive multivisceral involvement.[37]

Also in our patient an acute myeloid leukaemia chemotherapy regimen was performed because of the aggressive course of the disease and the presence in the bone marrow smears of > 20% of atypical mast cells even if circulating mast cells were not detectable.

We obtained initial improvement of general condition with remission of fever and reduction of organomegaly, but during the phase of bone marrow aplasia fever reappeared and multiple pulmonary infiltrates compatible with mast cell infiltration developed; during the phase of bone marrow recovery there was severe alteration of coagulation parameters with bleeding. At autopsy there was diffuse, massive infiltration of mast cells in tissues and signs of bleeding in central nervous system and gastro-intestinal tract.

Our case shows that systemic mastocytosis, because of its heterogeneous clinical picture, can mimic many disorders and diagnosis may be mistaken unless specific histological stains are performed. Poor sensibility to present chemotherapeutic drugs makes this disease, when presenting with aggressive course, difficult to treat and new therapeutic strategies are requested.

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