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Coexistent systemic mastocytosis and essential thrombocythemia complicated with monoclonal gammopathy and hypocomplementaemia

Case report

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Abstract: Hematological neoplasms associated with systemic mast cell disease are most frequently of myeloid origin. There are a few reports, however, of systemic mastocytosis (SM) cases associated with lymphoid or plasma cell neoplasms as well. In this report, the authors present a case of SM (with D816V mutation in the c-KIT gene) associated with JAK2 V617F mutation negative essential thrombocythemia. The leading symptom of the 78-year-old female was recurring hydrothorax that responded only to interferon alpha therapy. During the first year of therapy, the patient developed insulin-dependent diabetes and hypothyroidism. The hematological workup also revealed IgG kappa monoclonal gammopathy that was non-progressive in the following next three years. Low levels of complements without known clinical significance accompanied the entire picture.

Keywords: *Systemic mastocytosis • Monoclonal Gammopathy • Interferon alpha • Hypocomplementaemia*

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1. Introduction

Systemic mastocytosis (SM) is a rare disease. However, the diagnostic criteria and characteristic symptoms are well described [1,2]. Although hematological neoplasms associated with systemic mast cell disease are most frequently of myeloid origin, there are a few reports of systemic mastocytosis (SM) cases associated with lymphoid or plasma cell neoplasms [3-8]. The peculiarity of the present case lies in its association with both myeloid (essential thrombocythaemia, ET) and lymphoid (monoclonal gammopathy, MGUS) disorders. The therapy of SM is mainly based on the condition of c-kit: if mutated, tyrosin kinase therapy is ineffective and then alpha interferon (IFNα) should be the choice. Targeted therapy holds promise of a symptom-free condition. In this report, recurring hydrothorax that caused dyspnoea could be overcome only with administration of IFNα. Laboratory alterations, like cytopenia and other medical problems, emerged in the treatment course that might be related or unrelated to the basic underlying disease of SM. It is crucial to uncover the mechanism of their origin to provide the best treatment for the patient.

2. Case report

We present a case of a 78-year-old female who had been referred to our Semmelweis Mastocytosis Reference Center in April 2007 after the diagnosis of SM in association with ET (SM-AHNMD) had been verified

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elsewhere by trephine biopsy analysis. On physical examination, the skin manifestations of the disease could be seen in the form of sparsely appearing brownish tissue proliferations on the trunk and extremities. The liver and the spleen were enlarged, but no palpable lymph nodes were found. In summary, the hallmark of the disease was recurring hydrothorax that responded only to IFNα therapy. Additional co-morbidities emerged in the course, including insulin-dependent diabetes, hypothyroidism and IgG kappa type monoclonal gammopathy (MGUS) that will be further discussed in detail.

In the family history, her father died from acute leukaemia and her daughter developed large B-cell mediastinal lymphoma. From 1996, at the age of 67, the patient had a high thrombocyte count treated by aspirin. Her WBC and RBC counts were at that time in the normal range, but the platelet count varied between 683–878x10^9/L until 2005, when with the parallel decrease of RBC parameters (RBC: 3.5–3.75 x10^{12}/L; HCT: 32–35%, Hgb: 11.0–12.5 g/dl) an increase in MCV up to 100–103 fl was observed, and the platelet count declined slightly below normal level. In December 2006, she presented with dyspnoea and splenomegaly. A large amount of pleural fluid was seen on the chest X-ray on the left side that completely obscured the lower half of the lung and the left border of the heart, and caused a moderate contralateral mediastinal shift (Figure 1). The pleural fluid was drained, but it recurred and was drained repeatedly in the amount of 1.8 to 3.2 litres at different occasions. The sediment did not contain malignant cells. The hydrothorax was refractory to diuretics and even talc pleurodesis was not successful. The diagnosis of SM was decided upon and an iliac crest biopsy was performed, attributing significance at that time to the scantily occurring skin lesions resembling urticaria

Figure 1. Chest X-ray. Large amount of pleural fluid was seen on the left side, completely obscuring the lower half of the lung and the left border of the heart, and causing moderate contralateral mediastinal shift. No abnormal parenchymal density on the right side.

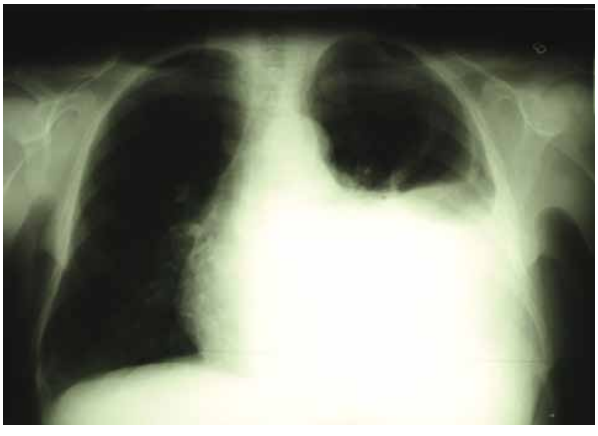

Figure 2. Confirmation of coexistant ET and SM on trephine biopsy.

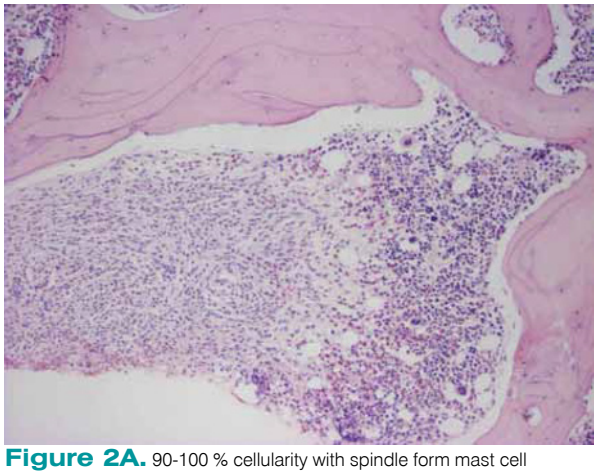

Figure 2A. 90-100 % cellularity with spindle form mast cell infiltrates and with grade 3 fi brosis.

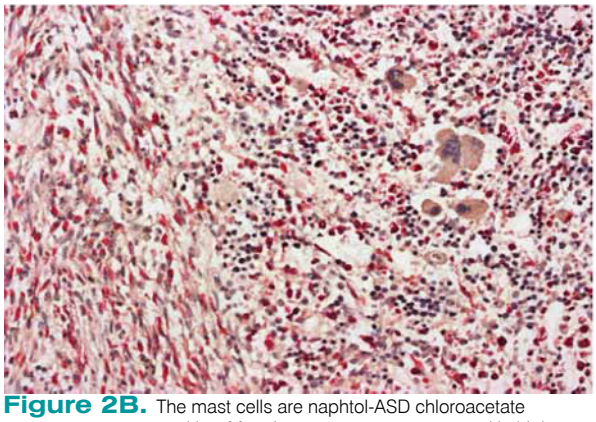

Figure 2B. The mast cells are naphtol-ASD chloroacetate pozitive. Megakaryocytes are represented in high number in different size and degree of maturation.

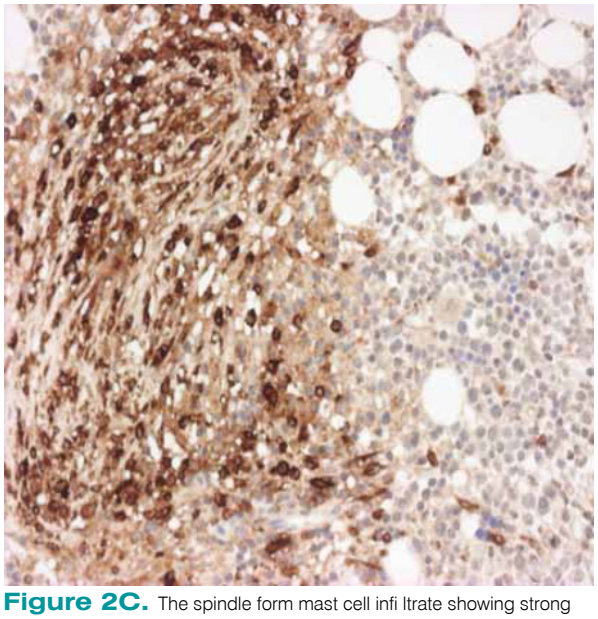

Figure 2C. The spindle form mast cell infi ltrate showing strong tryptase positivity.

pigmentosa. A bone marrow histology analysis identified SM coexistent with ET (Figure 2). Molecular studies revealed the presence of the D816V c-KIT mutation on exon 17. The disease was JAK2 V617F mutation negative and no bcr/abl gene rearrangement was present. The karyotype was 46, XX. TCRy gene rearrangement-, Immunoglobulin heavy chain rearrangement- and FIP1L1-PDGFR alpha fusion for del(4)(q12) studies were all negative. Serum tryptase level was 200 ng /ml (N(normal) < 20 ng /ml). Serum alkaline phosphatase was in the normal range at 158 U/l.

The highest platelet count was 985x 10^9/l before treatment with IFN α therapy had been initiated at a dose of 3 MIU three times per week from April 2007; after that, the pleural effusion did not recur. The workup of the macrocytic anemia resulted in normal values for vitamin B12, folate and TSH. A bone scan revealed age-related osteoporosis.

In December 2007, the patient felt unwell when her well-controlled type 2 diabetes progressed into an sudden-onset insulin-dependent form. The glutamic acid decarboxylase antibody (GADA) was negative, excluding an immune mechanism. C-peptide results were 1.61- and 2.05 ng/ml (N: 0.80–4.20) at two different time points in May, 2008 and in February, 2009, revealing that the patient's own insulin secretion was still present.

A few months later, in March, 2008, high TSH 5.3 mIU/L (N: 0.55–3.75) and low peripheral hormone levels (T3: 1.3 pmol/L (N:1.9–5.7) FT4: 9.1 pmol/L (N:10.0–22.0) were found and thyroid hormone replacement therapy was started. At this point, the anti-thyroid peroxidase antibody was 2 U/ml (N: 0–35) and anti-thyroglobulin antibody was 13 U/ml (N: 0–225), both within the normal range as determined by ELISA. Other antibodies, like those against mitochondrial-, smooth muscle-, liver protein-, reticulin fiber-, parietal cell- or collagen antigens, were all also negative. The anaemia did not respond to hormone replacement, therefore, in February 2009 as a part of a haematological workup, immunoglobulin analysis was performed. The results were as follows: IgA 1.43 g/L (N 0.70–4.00) IgG 23.26 g/L (N: 7.00–16.00) and IgM 1.83 g/L (N: 0.40–2.30). On immunofixation, IgG kappa monoclonal protein was found; its concentration did not change in the following three years. Urine analysis revealed non-significant proteinuria of 237mg /d and the presence of free kappa light chains. In our mastocytosis reference centre, complement analysis is performed whenever mastocytosis is suspected. Complement parameters in serum samples of the patient were measured every second month. In this case, we found continuous low levels of the classical pathway activity of complements characterized by depressed CH50, C4, C3, antigenic concentration of C1-inhibitor by methods used worldwide [9-11]. The level of C1q was normal. We could not detect antibodies either to C1-inhibitor or to C1q (Table 1**).**

Table 1. Complement parameters measured in every second month in 6 different serum samples

	Normal range	patient's samples n=6
CP, CH50U/ml	48-103	46.5* (42-52.5)
C1q, mg/l	60-180	250 (152-250)
C4, g/l	0.15-0.55	0.16 (0.13-0.27)
C3, g/l	0.70-1.80	0.60 (0.34-0.71)
$C1INH_f$, %	70-105	83 (73-90)
C1INH, g/l	0.15-0.30	0.13 (0.13-0.16)
anti-C1INH (IgG), AU/ml	0-2.0	0 (0-0.1)
anti-C1INH (IgA), AU/ml	0-0.6	0 (0-0.1)
anti-C1INH (IgM) AU/ml	0-12	1 (0.5-2.5)
anti-C1q (IgG), Au/ml	0-52	6.5 (4-9.5)

** median (interquartile range)*

Therefore, a complement consumption test was performed to determine whether the patient's sera contained complement-consuming factors. By this method, we did not find a depressed rate of the classical pathway activity of test samples expressed in the percentage of control samples (96% [79%–99.5%] median interquatile range), meaning that there was no complement consuming factor present.

3. Discussion

Mastocytosis is a rare disorder related to the autonomous proliferation and activation of mast cells; the classification of the disease distinguishes between cutaneous and systemic forms. The systemic form often coexists with other so-called non-mast–cell haematological disorders (SM-AHNMD) [12].

The majority of SM-AHNMD (80%–90%) cases are of myeloid origin; however, there are reports on SM associated with plasma cell dyscrasias as well [3-8]. In the present case, the patient had SM in association with both myeloid and lymphoid disorders. Although the reproduction of hydrothorax could be stopped by the administration of IFNα, new problems emerged during the treatment course – such as thrombocytopenia – that could be considered an SM C-finding. This consideration might also be applied for the macrocytic anemia – also occuring later in the course – that was not related to hypothyroidism, but might be a manifestation of ET as well.

The occurrence of autoimmune diseases in patients on IFNα therapy has been reported in several studies,

including autoimmune thyroiditis, thrombocytopenia and anaemia. The primary mechanism would presumably be the emergence of autoantibodies to various structural proteins or receptors [13]. In the present case, however, antibodies to the structures of thyroid (TRAK, TPO), insulin (GADA) or gastric parietal cells could not be demonstrated.

Concluding remarks and proposal for consideration:

The case presented here serves as a rare example of systemic mastocytosis coexisting with both myeloid- and lymphoid-proliferative disorders.

It is always questionable how to view thrombocytosis in association with SM. Thankfully to previous diagnostic criteria, if there is a significant raise in thrombocyte count and there are increased numbers of enlarged and mature megakaryocytes without fibrosis on trephine biopsy specimen together with mast cell infiltrates,the diagnosis of SM coexistent ET is more likely to be confirmed [14]. Cytopenia emerging in the course of SM might not necessarily be related to the underlying disease but could also be a symptom of hormonal deficiency or other coexistent disease as well that should be investigated.

A decreased C1-inhibitor (INH) level is not pathognostic for SM, in contrast to acquired angioedema resulting from C1-INH deficiency. There are examples in the literature of the coexistence of multiple myeloma and C1 INH deficiency that resulted in characteristic syndromes of angio-oedema. It has been therefore hypothesized that complement insufficiency/C1-INH deficiency itself might contribute to the development of lymphoid proliferation [15-17].

It remains a question, however, to what extent acquired C1-INH and hypo-complementaemia might contribute to mastocyte activation syndrome in general or in the development of pleural effusion, in the present case at least.

Protein analysis had not been performed before the initiation of IFNα therapy, thus the time of onset of MGUS remains uncertain. We therefore conclude that the determination of immunoglobulin profile of SM patients at the time of diagnosis, or at least before alpha IFNα therapy starts, would be helpful. Careful monitoring seems mandatory to evaluate the possible role of IFNα in inducing autoimmunity, and even MGUS, in a susceptible individual.

In the present case and in similar families at high risk for cancer, further complement studies would be interesting to perform to investigate the relationship to cancer development.

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