RESEARCH

Clinical and Molecular Diagnostic Evaluation of Systemic Mastocytosis in the South-Eastern Hungarian Population Between 2001–2013 – A Single Centre Experience

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Abstract Systemic mastocytosis (SM) is a rare chronic myeloproliferative neoplasm with only limited epidemiologic data published so far. We aimed to analyze the clinical and molecular diagnostic features, and the prognosis and cumulative incidence of SM cases in a cohort of south-eastern Hungarian patients of 13 year follow up. In the period 2001–2013, 35 consecutive SM cases were diagnosed in our regional centre. Immunophenotype, *KIT* D816V mutation frequency and clinical characteristics, and the prognosis impact of clinical subtypes were tested and compared with published data. Indolent SM (ISM) was diagnosed in 14 patients, SM with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD) in 15 patients and aggressive SM (ASM) in 6 patients. The *KIT* D816V mutation was found in 11/14 (78 %) of the ISM cases, in 12/15 (80 %) of the SM-AHNMD cases and in 5/6 (83 %) of the ASM cases. The life expectancy of ISM patients was better, whereas the SM-AHNMD and ASM groups exhibited a reduced median survival. The cumulative incidence for 13 year of the SM was 0.27/10,000. We detected lower 13 year cumulative SM incidence than of published epidemiologic data due to in our analyses involved only those patients who had bone marrow biopsy and histopathologically confirmed SM. This clinical overview clearly showed that the clinical characteristics differ between ISM (UP, anaphylaxis and osteoporosis) and SM-AHNMD/ASM (cytopenia, eosinophilia and splenomegaly).

Keywords Myeloproliferative neoplasm · Mastocytosis · *KIT* D816V mutation · Orphan disease

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Introduction

Systemic mastocytosis (SM) is a rare chronic myeloproliferative neoplasm characterized by morphologically and immunophenotypically abnormal mast cell proliferation in single or multiple extracutaneous organs [1–4]. To date only limited epidemiologic data have been published; the prevalence of SM in Central Europe has been estimated to be 0.5–1:10,000 [5]. Local regional data have been reported from Groningen on indolent SM (ISM) [6] and population based epidemiological data from Denmark [7]. The recently established centralized ECNM registry currently collects data from ten European countries, with the aim of comparing the incidence and biology of this rare disease in the regions and countries throughout Europe [8].

The 2008 World Health Organization (WHO) classification categorizes SM patients into various subtypes: ISM; SM with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD) for example acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML); aggressive SM (ASM);

mast cell leukaemia (MCL); mast cell sarcoma (MCS); and extracutaneous mastocytoma. On the basis of the histopathological findings and organ damage, a definitive variant the smouldering type of SM (SSM) was also introduced in 2007 [9]. The clinical presentation and prognosis in SM patients varies from indolent asymptomatic to an aggressive disease course. The symptoms can vary with the nature of the organ infiltration (e.g. anaemia, thrombocytopenia, malabsorption, hepato- and splenomegaly possibly causing a secondary organ dysfunction) or the mediator-related symptoms, such as cramps, flushes, diarrhoea or pruritus [10].

The diagnosis of SM is based on the presence of minor (such as the abnormal mast cell morphology in bone marrow; the expression of CD25 and/or CD2 in the abnormal mast cells; the presence of the KIT D816V mutation; the elevated serum total tryptase level) and major (the presence of multifocal clusters of morphologically abnormal mast cells in the bone marrow) criteria [11, 4]. The KIT D816V gain-of-function mutation, a substitution of aspartate (D) to valine (V) at position 816 in the kinase domain, found on exon 17, can cause autoactivation of the KIT receptor tyrosine kinase [12, 13]. However, this mutation is not specific for mastocytosis: it has also been reported in gastrointestinal stromal tumours, acute myeloid leukaemia and germ cell tumours [9, 14, 15]. The most of adult SM cases exhibit this mutation [12, 16].

It has recently been reported that the presence of KIT D816V may be sufficient to cause ISM but not ASM, though it is still questionable whether this mutation alone could be responsible for the diverse clinical presentation of mastocytosis [17, 11]. Interestingly it has also been established that the presence of the KIT D816V mutation in all haematopoietic lineages and the presence of elevated beta2 microglobulin levels are associated with a more aggressive form of mastocytosis, and might be identified as possible predictors of the disease progression [18, 19].

The KIT D816V mutation can cause resistance to imatinib mesylate [17, 20, 18]. In contrast, the wild-type KIT and several rare KIT mutations such as F522C and V559G have been demonstrated to be imatinib-sensitive [21].

The aim of this work was to calculate the 13 year cumulative incidence of the SM in a south-eastern hungarian haematological clinical centre and to survey the immunophenotypes, the KIT D816V mutation frequency, the clinical characteristics and the life expectancy in each subtype and in each case of SM cases which diagnosis were established on bone marrow biopsy in the last 13 years (2001–2013). At the time of this survey, the centre catered for 1,103,463 inhabitants aged 15 years or more from south-eastern Hungary [22].

Patients and Methods

Patients and Data Collection

Our centre is a regional centre that caters for the population of three counties in south-eastern Hungary, Southern Great Plain on map (Fig. 1). Our data originated in part from medical database of our centre, sorting with the ICD code (International Classification of Diseases, ICD-10) outpatient database and the inpatient database, and in part from the bone marrow biopsy findings assessed by the tumour pathology laboratory.

C-KIT mutation examinations are made on every bone marrow biopsy sample evaluated at our centre. Only those cases are considered to involve SM which comply strictly with the WHO 2008 criteria (1 major+1 minor or at least 3 minor criteria together). In Hungary, serum tryptase level measurement is currently still not available, but (even without the determined tryptase levels) all of our presented cases meet the WHO criteria of 2008.

Fig. 1 Introduction of the area of our regional centre in Hungary that caters for the population of three counties in south-eastern Hungary (Southern Great Plain)

Between 2001 and 2013, 35 patients were diagnosed with SM (15 females and 20 males with a median age of 57 years, range: 31–85 years): 14 with ISM, 15 with SM-AHNMD and 6 with ASM subtypes. All the haematological and pathological results on these patients were collected from the medical data files and reviewed with the approval of the Regional and Institutional Human Medical Biological Research Ethics Committee. Informed consent was not required. The study was conducted in accordance with the Declaration of Helsinki. The haematological management strategy was based on the current available recommendations at the time of the patient's diagnosis, and the therapy initiation [9, 23, 24, 11, 25, 17, 26–28].

Pathology

All bone marrow trephines were routinely fixed in Schaffer's fixative, decalcified in 12.5 % (*w/v*) pH 7.0 EDTA solution, and embedded into paraffin. Diagnostic immunohistochemical stains to CD117, CD25, mast cell tryptase, CD68, and phospho-STAT5 were made following a heat-induced antigen retrieval.

To detect *KIT* D816V mutation, polymerase chain reaction (PCR) was performed on each bone marrow trephine utilizing an allele-specific method (Schumacher) with modified parameters [29]. The results were validated by direct sequencing using an Applied Biosystems® 3500 DX Series genetic analyzer [29].

Statistical Analysis

Kaplan-Meier statistical analyses were made to evaluate the survival probability in the various SM subgroups (ISM, SM-AHNMD, and ASM) .

For each year we calculated the incidence rate as the number of new cases divided by the mid-year population size. The latter was calculated as the mean of the population size on 1st January on the relevant year and the next year. The cumulative incidence (CI) for 13 year was calculated as: $CI = 1 - e^{-\sum_{i=1}^{13} IR_i \cdot t_i}$, where IR_i denotes the yearly incidence rates from the 1st to the 13th year, and t_i denotes the length of each time period , which is 1 year in this case for all the 13 periods.

Results

The bone marrow biopsies revealed ISM in 14 patients (8 males and 6 females) with a median age of 55 years (range: 31–81 years). The median follow-up time was 50.5 months (range: 5–240 months). Cutaneous lesions (urticaria pigmentosa) were detected in 57 % (8/14) of the ISM patients. Mediator-related symptoms appeared in 28 % (4/14) of

them. The *KIT* D816V mutation was detected in 78 % (11/14). The main characteristics are introduced at Tables 1 and 2, while the detailed data on the clinical symptoms, the immunophenotypes, PCR and sequencing analysis in each patient are introduced in Supplementum 1 and 2.

SM-AHNMD was diagnosed in 15 patients (7 males and 8 females) with a median age of 57 years (range: 34–72 years). The median duration of follow-up was 25 months (range: 1–104 months). The bone marrow biopsy was indicated in these cases by the symptoms of the associated neoplasm, such as a bone lesion, or clinically relevant blood cell count abnormalities, for example eosinophilia or the elevated or decreased platelet or white blood cell count. This subtype of SM was associated with myelodysplastic syndrome (MDS) or with AML in 3 cases each, with myelofibrosis (MF) in 2 cases, or with ET, PV, chronic myeloid leukaemia (CML), hypereosinophilic syndrome (HES), multiple myeloma (MM), peripheral T-cell lymphoma (PTCL) or B-cell acute lymphoblastic leukaemia (B-ALL) in 1 case each. No cutaneous lesions or mediator-related symptoms were detected in these cases. The *KIT* D816V mutation was detected in 80 % (12/15). The detailed data on the individual SM-AHNMD patients are presented in Supplementum 1 and 2.

ASM was diagnosed in 6 patients (4 males and 2 females) with a median age of 65 years (range: 54–85 years). The median follow-up period was 20.5 months (range: 2–35 months). The indications of bone marrow biopsy in these cases were hepatosplenomegaly with or without pancytopenia/anaemia/eosinophilia and a weight loss. According to the WHO criteria at least one or more C findings (marked cytopenia; osteolysis with or without pathologic fractures; ascites and elevated liver enzymes; malabsorption plus hypalbuminaemia , palpable splenomegaly with hypersplenism) were present in all of ASM cases [23, 11]. Cutaneous lesions were observed in 33 % (2/6) of the patients. Mediator-related symptoms were present in 1 case. The *KIT* D816V mutation was detected in 83 % (5/6) of the patients. The detailed data are to be seen in Supplementum 1 and 2.

The survival data of each SM subtype according to Kaplan-Meier survival curve analysis are presented in Fig. 2.

The median survival for the ASM group was 1.73 years, while that for the SM-AHNMD group did not reach the median during the observed follow-up period. No patients died during the follow-up period in the ISM group. The Mantel-Cox, Breslow and Tarone-Ware tests uniformly led to *p*= 0.000, demonstrating that the survival differed significantly in the observed subgroups.

Our regional medical university centre receives SM patients from among 1,103,463 inhabitants aged 15 years or more in south-eastern Hungary [22], and this allowed to calculate the cumulative incidence for 13 year of the of SM in general population, which proved to be 0.27/10,000 in this region.

Table 1 Main clinical characteristics of the patients

Characteristics	ISM	SM-AHNMD	ASM
Patients (N)	14	15	6
Males (N)	8	7	4
Females (N)	6	8	2
Median age at diagnosis, median (years) (range)	55 (31–81)	57 (34–72)	65 (54–85)
Median follow up (months) (range)	50.5 (5–240)	25 (1–104)	20.5 (2–35)
Associated haematological disease	none	MDS(3);AML(3);MF (2); ET(1); PV(1);CML(1); iHES(1);MM(1);PTCL(1); B-ALL(1)	none
Urticaria pigmentosa	8/14	none	none
Mediator-related symptoms: skin (S) gastrointestinal (GI) cardiovascular (CV) neurological (N) anaphylaxis (A)	S: 5/14; GI: 3/14; CV: 2/14; N: 1/14; A: 2/14	none	S: 2/6; N:1/6
Coexistent allergy (inhalative, nutritive, drug, insect)	3/14	none	none
Constitutional symptoms	2/14	1/15	6/6
Organ damage / organopathy: Hepatomegaly (H), Splenomegaly (S), Adenopathy(A), Osteopenia/ osteoporosis/osteolysis(O)	H: 2/14; H*: 1/14; A: 1/14; O: 3/14	H: 3/15; S: 2/15; A: 1/15	H*: 6/6; S: 3/6; A: 3/6; O: 3/6
C findings	none	none	6/6

Abbreviations: *ASM* aggressive systemic mastocytosis; *ISM* Indolent systemic mastocytosis; *SM-AHNMD* systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease;mediator- related symptoms; *S* skin (flush, pruritus); *GI* gastrointestinal symptoms (diarrhoea); *CV* cardiovascular (palpitation, dizziness, syncope); *N* neurologic; *A* anaphylaxis; Constitutional symptoms were observed generalized weakness, fatigue, sweats, chills, arthrarlgias, myalgias; Organ damage/ organopathy: hepatomegaly (H) H*: hepatomegalia with elevated alkaline phosphatase; spleno- megaly (S); Adenopathy (A);Osteopenia/osteoporosis/osteolysis (O);iHES: idiopathic hypereosinophilic syndrome; MDS: myelodysplastic syndrome; AML: acute myeloid leukaemia; ET: essential thrombocythaemia; MM: multiple myeloma; MF: myelofibrosis; PTCL: peripheral T-cell lymphoma; CML: chronic myeloid leukaemia; B-ALL: B-cell acute lymphoblastic leukaemia; PV: polycythaemia vera

Four patients (cases 2, 13, 29 and 35) were excluded from this cumulative incidence estimation: although they were di- agnosed in our regional centre, they were not inhabitants of this region of Hungary.

Discussion

The aim of this paper was to summarize our clinical experi- ence in SM in the period 2001–2013. Since there is no official national mastocytosis registry in Hungary, we aimed to use our regional data to calculate the cumulative incidence of SM in a south-eastern hungarian clinical centre, based on only those cases (introduced above) which were referred to histo- pathological analysis of bone marrow biopsy and the presence of SM were confirmed.

Our analyses demonstrated that the main cause of the indication of the bone marrow biopsy in the group of ISM patients was urticaria pigmentosa (8/14; 57 %). It is im- portant, therefore, that the dermatologist should refer the patients to haematological centres to establish the poten- tial bone marrow involvement in the presence of cutane- ous mastocytosis lesions. In other cases, the bone marrow biopsy was indicated by eosinophilia (3/14; 21 %), anae- mia (1/14; 7 %), lytic bone lesions (1/14; 7 %) or adenomegaly (1/14; 7 %).

Table 2 The main characteristics indicating bone marrow biopsy, and the main results

Subgroups	Main clinical symptoms /findings/features	KIT mutation (PCR) D816V(+)	BM dysplasia	BM fibrosis	BM eosinophilia
ISM	urticaria, anaphylaxis,osteoporosis	11/14	1/14	0/14	6/14
SM-AHNMD	cytopenias, splenomegaly,	12/15	5/15	3/15	3/15
ASM	cytopenias, splenomegaly, eosinophilia	5/6	1/6	0/6	3/6

Abbreviations: *ASM* aggressive systemic mastocytosis; *BM* bone marrow; *ISM*: Indolent systemic mastocytosis; *SM-AHNMD* systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease

Fig. 2 Survival of systemic mastocytosis patients classified by disease type. The observed Kaplan-Meier survival for systemic mastocytosis patients classified by disease type: ISM (blue), SM-AHNMD (green), and ASM (yellow)
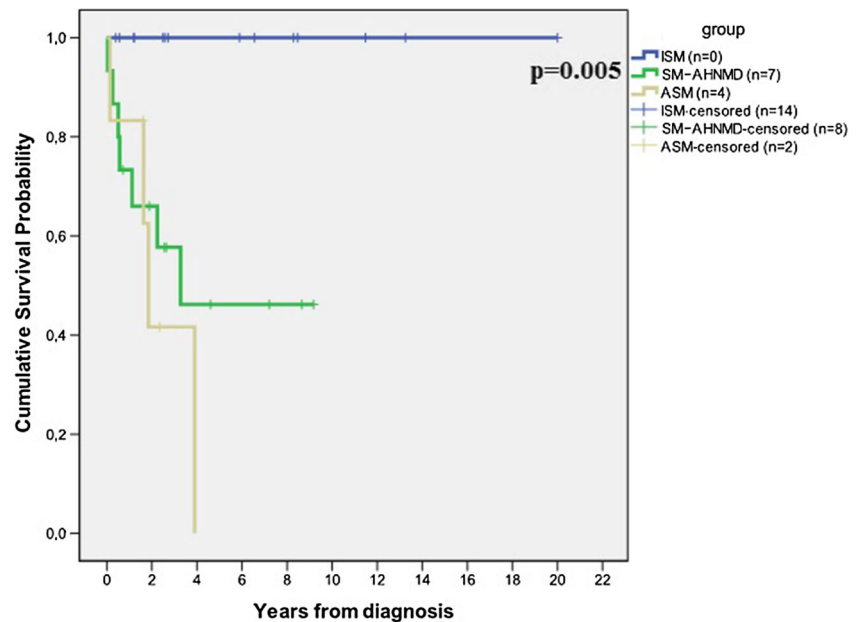
In the SM-AHNMD cases, it was predominantly the symptoms of the associated neoplasm that indicated the bone marrow biopsy. In the majority of our patients (14/15; 93 %), these were symptoms of pancytopenia, anaemia, leukocytosis, thrombocytosis, bone pain/lesion or hepatosplenomegaly. In one case, attention was drawn to the associated SM by the lymphoma staging process. Our finding was consistent with previous reports [16] whereas the most common associated clonal diseases was myeloid neoplasms (12/15 cases; 80 %) and the associated lymphoid neoplasms was much less common (3/15 cases; 20 %).

In the ASM subgroup, the bone marrow biopsy was indicated in all cases (6/6; 100 %) by anaemia with or without thrombocytopenia or hepatosplenomegaly with or without constitutional symptoms.

It has been reported [9] that ISM is mostly associated with cutaneous symptoms and this is in agreement with our own findings (8/14 cases; 57 %), whereas we observed a lower rate of these associations in ASM (2/6; 33 %), and there were no such cases in SM-AHNMD.

Only the *KIT* D816V mutation was detected among our cases, with a frequency close to the reported data [30]. This mutation was positive in 78 % (11/14) of the ISM cases, 80 % (12/15) of the SM-AHNMD cases, and 83 % (5/6) of the ASM patients.

Lim et al. concluded that the life expectancy in ISM was superior to that in non-ISM, and not significantly different from that for the age- and sex-matched US population, a result that validated the prognostic relevance of the WHO subclassification of SM [16]. A long-term study of the Spanish Network on Mastocytosis also led to the finding that the great majority of adult ISM patients have a normal life expectancy

[19]. Our analyses of Hungarian patients revealed that the survival rate of SM patients is less than that expected for the age- and sex-matched Hungarian population; The life expectancy of the patients with ISM was excellent, whereas the SM-AHNMD and ASM groups exhibited a reduced median survival. This distribution of subtypes and survival pattern in our study was similar to previously published in the Mayo clinic study [17].

The recently established centralized ECNM registry currently collects data from ten European countries, and epidemiological data are already therefore available as concerns the prevalence of SM [8]. The prevalence of mastocytosis in Central Europe has been estimated to be ~0.5–1/10,000 [5]. Our findings of the 13-year cumulative incidence of SM in general population aged 15 years or more was 0.27/10,000 fit the incidence of orphan diseases. As in the most relevant literature, we can not report a gender predominance [5].

Limitations

Since only cases that complied strictly with the WHO criteria were included as SM cases, the cumulative incidence of SM calculated during our research is likely to be somewhat underestimated. On this basis, the 13-year cumulative incidence of SM in our research was 0.27/10,000, and only the clinical features of this group of patients were considered.

Only the SM cases were enrolled in our detailed investigation. Those patients with skin lesions, who refused the BM biopsy, were not enrolled in our calculations.

The cumulative incidence would be increased by inclusion of the patients (3) with only two minor criteria (whose data are not included in the present manuscript), whose serum tryptase

examinations may later lead to some of them fulfilling the three minor WHO criteria.

The real cumulative incidence might be higher because SM is often underdiagnosed and the symptoms can be subtle or absent.

Conclusion

This clinical overview clearly showed that the clinical characteristics differ between ISM (UP, anaphylaxis and osteoporosis) and SM-AHNMD/ASM (cytopenia, eosinophilia and splenomegaly).

Despite the existence of the centralized ECNM registry and the avaliability of some epidemiological data on the incidence and prevalence of SM, the lack of an official national mastocytosis registry in Hungary led us to apply our regional data to calculate the cumulative incidence of SM in southeastern Hungary. This cumulative incidence of SM in adults was lower compared to the epidemiologic data reported in the literature due to in our analyses involved only those patients who had bone marrow biopsy and histopathologically confirmed SM [6].

Competing interests The authors declare that they have no competing interests.

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