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TMS Grant Launches Mastocytosis Registry at Brigham & Women's Hospital

- **Regis (Gigi) Park, Former Research Committee Chair**

It has been a pleasure and a privilege to work with The Mastocytosis Society. I have shared with all the patients their concerns, symptoms and daily disappointments and sometimes joys. I have learned much from all of you about this fascinating disease. Much work is to be done, but I am proud to say that The Mastocytosis Society has now established a landmark and that the Mastocytosis Registry is the start of a promising future for all Mastocytosis patients.

- **Dr. Mariana Castells, Mastocytosis Registry Coordinator**

Introduction

In the fall of 2002, The Mastocytosis Society (TMS) received a very special gift from the family of Kristin L. Forest. Kristin is a long time member of TMS, and past president. Her parents, Dean and Roberta Smith, had given generously to the organization on several occasions, even asking for donations to TMS in lieu of gifts for their 50th wedding anniversary. Sadly, Dean Smith passed away in 2000 and Roberta Smith in 2001. In a conversation with her daughter, Kristin, Mrs. Smith stated that the couple regretted not being able to turn their full attention to finding a cure for Mastocytosis. In a final act of unparalleled generosity, Mrs. Smith donated the proceeds from the Smith's 401K retirement account toward that end—a gift totaling \$16,100.42.

This donation constituted a grant awarded to Dr. Mariana Castells of Brigham and Women's Hospital in Boston, MA, for the purpose of forming a comprehensive Mastocytosis Registry. This registry was designed with the ability to integrate information from other research centers – a feature which distinguishes it from other databases. In a recent interview with Dr. Castells, she stated that the formation of a central registry for arthritis had resulted in major advances in the treatment of that disabling disease. It is her hope that by integrating data to form a central registry based at Brigham and Women's, the same progress might be made in the treatment of mast cell disease.

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What follows is Dr. Castell's report on the use of the grant and the considerable progress that has been made thus far. As a result of the work of Dr. Castells and her colleagues, Mast Cell Mediators Activation Syndromes has been added as a suggested disease category – a development which should have a profound impact on the large number of TMS members who do not fit the current criteria for the diagnosis of mastocytosis. At present, Mast Cell Mediators Activation Syndrome is not an official disease category and consensus among the different groups who work on mastocytosis will be needed. Dr. Castells is hopeful that ongoing studies at the NIH and other research centers, all of which support the findings of patients with subtle bone marrow abnormalities who do not meet the Vienna criteria, will soon yield the adoption of this proposed name or a similar classification to address these patients.

Among other things, Dr. Castells stresses the need for further funding to study the natural history of Mast Cell Mediators Activation Syndromes and its potential progression to Systemic Mastocytosis. Unfortunately, funding for the project has run out, but Dr. Castells hopes to garner support from colleagues and patients alike for this landmark project. So, Mr. and Mrs. Smith, you may not have seen a cure for mastocytosis in your lifetimes – but you've given us a significant starting point. For this, we are truly grateful.

Mastocytosis Registry Grant Report to The Mastocytosis Society

Dr. Mariana Castells
Brigham and Women's Hospital
Boston, MA
Date: June 30th, 2004

A. Brief Summary of how the grant was used:

We proposed to study the clinical course of mastocytosis (natural history), in which the first step was to establish a Registry based at the Brigham and Women's Hospital, with a longitudinal follow-up. The Registry was aimed at collecting patients with Mastocytosis, from the clinics of Dr Castells, Austen, Horan, Sheffer and from the on-line Registration Form distributed through the Mastocytosis Society. For the past 40 years the Mastocytosis Clinic at the Brigham and Women's Hospital has been a referral center for patients with Mastocytosis and accounts for the greatest source of referrals in Massachusetts.

1. Human Research Committee Proposal:

A Human Research Committee Proposal for the acquisition of data from patients was generated and submitted for approval to the BWH Human Research Committee. Patient protection was ensured by a confidentiality agreement and the three basic ethical Belmont Principles of respect, beneficence and justice were applied to all interactions with patients and to the data collection. The IRB was approved and activated, and will run until 10/09/2004.

2. Registry Form:

A Registry Form was elaborated by the PI and modified with the help of the Biometry and Methodology Core of the Division of Rheumatology, Immunology and Allergy. The Registry Form includes clinical presentation, tissue diagnosis with disease markers as established in the Consensus Diagnostic Criteria (1), treatment and disease progression since diagnosis. Clinical presentation includes all symptoms associated with mastocytosis as follows; constitutional, cutaneous, gastrointestinal, cardiovascular,

skeletal, pulmonary, neurological and psychiatric. Procedures to evaluate organ systems include CT scans, bone scans, GI examinations. The tissue diagnosis includes bone marrow biopsy and aspirate, skin biopsy and biopsy of any tissue in which the presence of mast cell is assessed with the standard Giemsa and tryptase stains. Disease markers include tryptase, soluble CD2, CD25 and IL-6 in serum; PGD2 and histamine in urine. Medication is recorded with doses. Abnormal laboratory values are recorded. Surgical procedures, complications, pregnancy and child delivery are recorded. Females are evaluated for fertility. Families with multiple members presenting familial mastocytosis are included in the Registry.

3. Data Collection:

The data has been collected either directly from the patients at the time of their doctors appointments or from the e-mail Registry Form completion by Dr Paari, the Research Assistant assigned to the Registry Grant. Before entering the Registry Dr Paari informed all patients of the purpose of the Registry and its implications. He reviewed BWH medical charts, and for patients outside the BWH, he contacted them by phone. Dr Paari, a computer expert, collected the data from 82 patients and entered it in the BWH computer register as permanent data collection. Preliminary analysis of the data has been done on the 82 patients.

B. Brief Summary of outcomes achieved as a result of the grant:

Because new research indicates that Mastocytosis has a spectrum of presentations and patients who do not qualify for the diagnosis of Mastocytosis by the Vienna criteria can present with Mast Cell –Mediator Activation Syndromes and can have subtle Bone Marrow abnormalities, we added a special Category to the Registry. Mastocytosis was classified into 8 categories as follows: Cutaneous Mastocytosis, Indolent Systemic Mastocytosis, Systemic Mastocytosis with hematological malignancy, Aggressive Systemic Mastocytosis, Mast Cell Leukemia, Mast Cell Sarcoma, Extracutaneous Mastocytoma and Mast Cell Mediators Activation Syndromes.

Preliminary Registry Data:

Cutaneous Mastocytosis: 27 patients
 Indolent Systemic Mastocytosis: 36 patients
 Systemic Mastocytosis with non-mast cell Hematological Malignancy: 3 patients
 Aggressive mastocytosis: 3 patients
 Mast Cell Leukemia: 1 patient
 Extracutaneous Mastocytoma: 1 patient
 Mast Cell Sarcoma: none
 Mast Cell Mediators Activation Syndromes: 11 patients

C. Future Plans for the program:

The incidence and prevalence of Mastocytosis is still unknown as well as its natural history. There is no cure for Mastocytosis at the present time. The initial report from the Registry suggests that over 95% of the patients have either indolent or cutaneous disease, which has a generally favorable prognosis. Morbidity due to symptoms derived from mast cell mediators release is still high, despite intense therapy with multiple medications aimed at blocking mast cell mediators. Symptoms such as flushing, pruritus, urticaria, episodes of hypotension and syncope, gastrointestinal pain and diarrhea and neurological symptoms (2) are found in great proportion in the Registry patients. A mixed organic brain syndrome, which was originally described in our institution (3), is present in high proportion of patients in the Registry. Interstitial cystitis is now recognized as driven by mast cell infiltration and release of mediators and female sufferers are predominantly affected (4).

Future plans include the need of further funding to analyze:

1. The impact of medication in mast cell mediator-derived symptoms in mastocytosis
2. The quality of life of patients with mastocytosis
3. The evolution of signs and symptoms during the course of mastocytosis
4. The natural history of Mast Cell mediators Activation Syndromes and its potential progression to Systemic Mastocytosis.

Mastocytosis research has advanced in the last 10 years, with a better understanding of the pathogenesis and of the mediators involved but treatment options are often empirically offered and new therapeutic modalities are not integrated due to lack of evidence-based benefits. This Registry will help understand its clinical presentation, course and response to mediator-related and immunomodulatory therapies of patients with the various forms of Mastocytosis. It will also offer the possibility of establishing Clinical trials of new medications in a given patient population.

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