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Difficulties in diagnosis and management of mastocytosis in clinical practice and role of patients' associations

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Abstract

Mastocytosis is a heterogeneous group of disorders characterized by abnormal expansion and accumulation of mast cells in one or more organs. It is a rare disease, with uncertain prevalence in many countries. The diagnosis and management of rare diseases, including mastocytosis, rise many problems in clinical practice, mainly due to limited medical information and low attention from health care givers. Misdiagnosis of mastocytosis is frequent, mainly due to low prevalence, versatile clinical picture, addressability to many specialists and confusion with various types of allergies. Beside delayed diagnosis, patients with mastocytosis face expensive investigations, unavailable treatment options, risk of complications and impaired quality of life. The aim of this paper is to evaluate the actual situation of mastocytosis patients in Romania, difficulties in diagnosis and management and main activities of patients' associations. Patients' associations have an important role in improving health assistance of rare diseases, such as mastocytosis, mainly in countries with less developed health system and when interdisciplinary approach is needed. We also aimed to point out patients' needs and expectations from medical staff and health authorities and to make a step forward to improved medical assistance of this rare disease, according to actual standards in European countries.

Keywords: mastocytosis, patients' associations, rare diseases

INTRODUCTION

Mastocytosis is a heterogeneous group of disorders characterized by abnormal expansion and accumulation of mast cells (MC) in one or more organs, with or without skin involvement (Arock M et al, 2010). It is a rare disease, with uncertain prevalence in many countries. The worldwide reported prevalence is between 1/40.000 and 1/20.000 (about 2,6 in 10.000 people), meaning below the ceiling for orphan designation, which is 5 people in 10.000 (European Medicines Agency, 2013). Systemic mastocytosis (SM) preferentially affects Caucasian adult population, with the average age at diagnosis of 60 years and with no sex predominance. Mastocytosis results from a clonal proliferation of morphologically and immunophenotypically abnormal mast cells, accompanied by the release of large amounts of histamine and other active mediators. The clinical picture and prognosis depend on the onset age, organs involved, clinical pattern, associated hematologic abnormalities and therapeutic response. In children, the disorder usually affects only the skin (cutaneous mastocytosis) and may cause a red and itchy rash. In some patients, mainly adults, the disorder progresses into systemic mastocytosis, in which mast cells infiltrate organs, such as gastro-intestinal tract, liver, spleen and bone marrow. Misdiagnosis of mastocytosis is frequent, mainly due to low prevalence, versatile clinical picture, addressability to many specialists with limited knowledge in allergology. Mastocytosis is a condition that is debilitating on long term and may be life threatening in those patients

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who develop the aggressive systemic form or complications, such as anaphylaxis. Early diagnosis of mastocytosis and correct treatment and monitoring are essential for better prognosis of affected patients and also for better quality of life of patients and their families.

Actual situation of rare diseases in Europe (European Commission Report to European Parliament, COM 2014)

Improved medical assistance of rare diseases is considered a key priority of health policy in European Union. Rare diseases are defined by prevalence below 5 in 10.000 persons, leading to chronic invalidity or risk of death and needing conjugate efforts for diagnosis and treatment. The level of knowledge and expertise in rare diseases are generally considered inadequate in many countries, with significant differences between European countries. In 2008 the European Commission (EC) has adopted the Communication "Rare diseases: a provocation for Europe" – General strategy to support member states in diagnosis and treatment of persons with rare diseases and in elaborating national strategies.

The Report of EC issued in 2014: Regarding application of Communication has main objectives: definition, codification and inventory, development of research and new therapies, European reference networks, homogenization of expertize in EU, responsibilisation of patients' associations, sustainability. There is an urgent need to improve codification of rare diseases, for better recognition in the next ICD 11 in 2017 (common action EUCERD). Some countries are already using ORPHA codification system for rare diseases based on ORPHANET.

History of concepts in mastocytosis

The mast cell was first discovered and described by Paul Ehrlich in 1876 and the disease mastocytosis was first described by Nettleship and Tay as a "Rare form of Urticaria" published in British Medical Journal in 1869. In 1949, Ellis discovered the involvement of the internal organs in mastocytosis in an autopsy case and ten years later the term mastocytosis was created (Ellis JM et al, 1949). A first classification of the disease was introduced by Lennert in 1979 (Lennert K et al, 1979) and in 1991, a first consensus classification was proposed by Metcalfe (Metcalfe DD et al, 1991). Between 1991-2000 many relevant cellular, molecular and biochemical defects resulting in mastocytosis were discovered and was proved that, at least in systemic variants, the accumulating mast cells are monoclonal (neoplastic) in nature. In 2001 the World Health Organization adopted both the diagnostic criteria and the classification of mastocytosis (Valent P et al, 2001). In 2002, the European Competence Network on Mastocytosis (ECNM) was created and in 2014 a diagnostic algorithm for patients with suspected mastocytosis was proposed, based on Austrian and Spanish Networks recommendations (published in *Allergy* by Valent P et al, 2014).

Diagnostic criteria and classification of mastocytosis

Depending on the organ(s) involved, mastocytosis can be divided into cutaneous forms (CM), systemic forms (SM) and localized MC tumors (Escribano L et al, 2002). The clinical forms of cutaneous mastocytosis are: urticaria pigmentosa (UP), diffuse cutaneous mastocytosis, telangiectasia macularis eruptiva perstans (TMEP) and solitary skin mastocytoma. Mastocytosis affects the skin in almost all pediatric cases and in about 80% of adult cases. The major variants of systemic mastocytosis are: indolent systemic mastocytosis (ISM), smoldering mastocytosis, isolated bone marrow mastocytosis and severe hematologic forms, with poor prognosis. These last categories are represented by aggressive SM, SM associated with clonal non mast cell hematologic neoplasia and mast cell leukemia. The clinical presentation may range from skin-limited disease, particularly in children, to various degrees of extracutaneous involvement, generally seen in adults (Sperr WR et al, 2012). Indolent systemic mastocytosis represents about 80% of all systemic forms and is usually characterized by symptoms related to mast cell degranulation and mediator release, mimicking clinical picture of allergies, sometimes severe, like anaphylaxis. Independent of the category of cutaneous or systemic mastocytosis, patients may suffer from mediator-related symptoms, which can be mild, severe or life-threatening (Castells M et al, 2002). Apart from mediator-related symptoms, patients may also suffer from osteopenia or osteoporosis, gastro-intestinal symptoms, neurological or psychiatric symptoms and/or symptoms related to skin lesions. In advanced mastocytosis, additional problems may develop, such as cytopenia, ascites, malabsorption, lymphadenopathy, splenomegaly, hepatopathy or large osteolysis with pathologic fractures (Delsignore JL et al, 1996). Clinical features suggesting mastocytosis

are: idiopathic anaphylaxis, severe anaphylaxis induced by Hymenoptera insects sting, unexplained pruritus and flushing, syncopes, advanced osteoporosis, neurologic or psychiatric signs and symptoms. Diagnosis of mastocytosis with skin involvement in adults (mastocytosis in the skin-MIS) is usually suggested by characteristic lesions, but the absence of skin lesions makes the diagnosis difficult, especially when the symptoms are non-characteristic. Monoclonality of mast cells in mastocytosis can be documented by demonstrating the presence of a point mutation in the c-kit proto-oncogene or abnormal expression of surface markers, such as CD25, CD2. In the majority of patients with systemic mastocytosis, the somatic c-kit mutation D816V(Asp-816-Val) is detected in the bone marrow and often also in skin lesions, while in a smaller group of patients with systemic mastocytosis, the mutation can also be found in peripheral white blood cells (Longley BJ et al, 1996). This constitutively activating mutation of mast cells is responsible for their spontaneous activation independent of ligand.

Laboratory confirmation of diagnosis is done based on increased serum tryptase level, bone marrow examination and detection of characteristic c-kit mutation. Serum tryptase, which is preferentially produced by activated mast cells, is an important biomarker used in diagnosis of mastocytosis and an important initial screen parameter in suspected mastocytosis without skin lesions (Valent P et al, 2013).

The main treatment recommendations are as follows (Pardanani A et al, 2013):

1. Avoidance of symptoms triggers such as: heat and humidity, emotional and physical stress, alcohol, medications (aspirin, opioid analgesics, radiocontrast agents etc.)

2. Therapy of systemic mast-cells mediator release: antihistamines H1 and H2, cromolyn sodium, leukotrienes antagonists, cytoreductive agents in refractory and more severe cases (interferon- alpha, cladribine, imatinib mesilate).

3. Evaluation and treatment of allergy and anaphylaxis, since the incidence of anaphylaxis in adult patients with mastocytosis is significantly higher than in general population (ranges from 20% to 49%).

4. Special attention and prevention in perioperative management

5. Management of Hymenoptera venom allergy and anaphylaxis

6. Evaluation and treatment of bone disease – early diagnosis and treatment of osteoporosis, usually with bisphosphonates.

European and American Mastocytosis Societies and networks

The European Competence Network on Mastocytosis (ECNM) was initiated in 2002 as a multidisciplinary and multinational cooperative

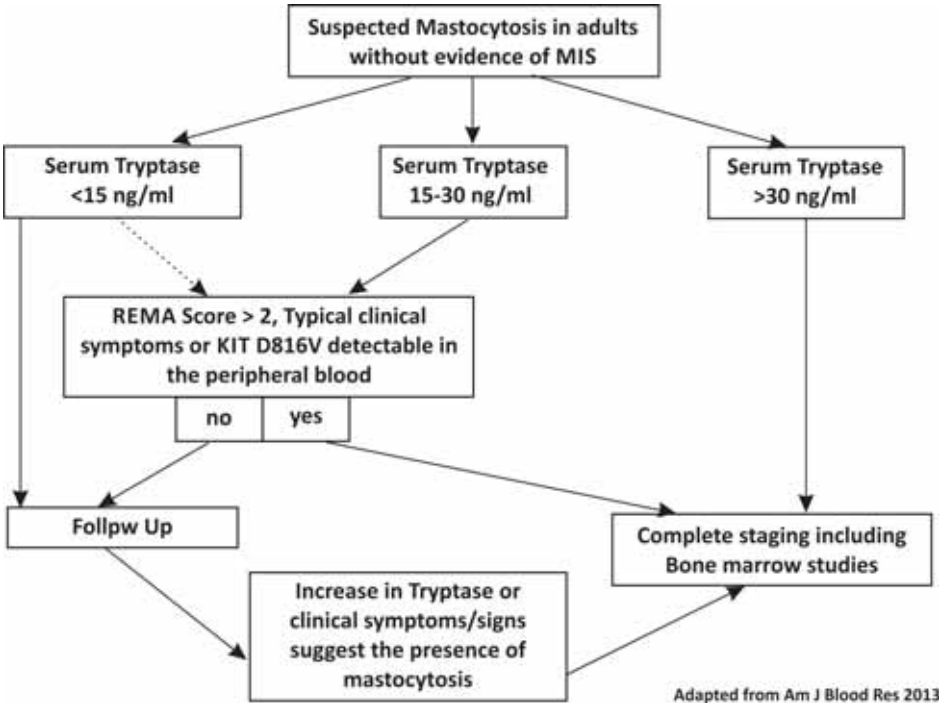

FIGURE 1. Diagnostic algorithm in suspected mastocytosis *(Am J Blood Res 2013, 3(2), 174-180) (Am J Blood Res 2013; 3(2): 174-180)*

approach to increase awareness and to improve diagnosis and therapy of mastocytosis (Valent P et al, 2012). ECNM has expanded to various countries and contributed successfully to the development of markers, definition and standards in the field of mastocytosis.

There are 25 Centers of Excellence for mastocytosis in Europe, beside other reference and cooperation centers and individual collaborators, who organize annual meetings, working group, coordinate management and patients registry (ECNM 2006 homepage on www.ecnm.net). There are five Centers of Excellence in Germany, two in France and Spain, three in Austria and Poland, one in Switzerland, Hungary, Turkey, Holland, England, Denmark, Greece, Italy, Sweden and Portugal. The Reference centers are highly specialized on a distinct issue or discipline relevant to the diagnosis, management or treatment of mastocytosis.

The Mastocytosis Society (TMS) from USA, member of The American Academy of Allergy, Asthma and Immunology and of National Organization of Rare Disorders, was founded in 1995 and is very active in supporting patients, spreading medical information and coordinating research in the field of mastocytosis (www.tmsforacure.org).

Role of patients' associations in Romania

The first Association of Patients with Mastocytosis from Romania was created in 2012 and the second one, named Association Support for Mastocytosis in Romania, followed in 2016, with the scope of helping patients to have access to investigations, diagnostic and treatment. Since in Romania there is no national reference center for mastocytosis, no network and no registry of patients, the patients' associations took some of the tasks of health workers. They made a site and announced patients to contact them, made a short movie with patients explaining their disease and initiated correspondence with the Ministry of Health, Insurance House and medical Commissions of Rare Diseases, Hematology, Dermatology and Allergology. They asked recognition of mastocytosis as rare disease and full reimbursement of therapies for all forms of disease. In 2014, they have organized the first Symposium on Mastocytosis, with the participation of a reputed European specialist – prof. Luis Escribano from Spain. The consequences of this event were seen during the next period, more specialists became interested of mastocytosis, some of them presented or published medical informations about this rare disease. The author of this paper gave a TV interview about mastocytosis, made a presentation during the National Allergology Congress, including information about patients association and initiated collaboration with other specialists from Romania and Europe. The Mastocytosis Commission of Health Ministry was created in 2015.

The mastocytosis patients succeeded to obtain their voice to be heard and had some remarquable achievements, but some requests are still pending, such as: inclusion of mastocytosis in the list of rare diseases, registration and reimbursement of all therapies, including sodium cromoglycate and other facilities for diagnosis and monitoring.

DISCUSSION

Situation of rare diseases, such as mastocytosis, is difficult in those countries with poor and less developed health systems. Both diagnosis and treatment of mastocytosis are difficult, mainly due to limited knowledge and low attention from health care givers. The case of mastocytosis is even more complicated by heterogeneity of disease, difficulty of diagnosis, need for interdisciplinary approach and various treatment options. The real prevalence of mastocytosis in Romania is not known, the number of recorded patients is very small and, according to prevalence data from other European countries, it should be more than ten times higher. For comparison with another European country, in Spain there are two excellence centers on mastocytosis, a strong Mastocytosis Society and Network and more than 2000 patients with mastocytosis are diagnosed and monitored (from a total population of about 47 millions inhabitants). We consider that many cases in Romania are ignored, maybe never diagnosed, since they have no access to specialist advice and investigations. Since many cases of indolent mastocytosis appear like or are complicated by severe allergies, the role of allergists in the multidisciplinary team should be reinforced. The recommendations of the European Competence Network on Mastocytosis (ECNM) regarding the diagnosis and treatment of mastocytosis should be implemented in all countries. Patients' associations have an important role in improving health care of rare diseases and their collaboration with medical societies and health authorities should be stimulated. Treatment of

mastocytosis should be adapted to clinical form and preventive therapies, such as sodium cromoglycate, should be preferred and facilitated in systemic indolent forms (Edwards AM et al, 2010).

CONCLUSIONS

We concluded that diagnosis and management of mastocytosis in Romania should be facilitated and improved , according to actual international recommendations. The role of patients' associations is important for improving health care of these patients, but it should not replace the institutional mandate of health authorities and medical staff. There is an urgent need to have a National Excellence Center for Mastocytosis, a National Registry of patients, to collaborate with ECNM and to implement actual guidelines for diagnosis and treatment of all forms of this rare disease. Role of different specialists in managing mastocytosis should be more clearly stated and interdisciplinary collaboration be improved. A special attention should be paid to indolent systemic mastocytosis, including reimbursement of all investigation procedures and treatment, introduction of protocols for medical assistance in special situations, such as anesthesia, surgery, anaphylaxis, insect stings and to preventive therapies, such as sodium cromoglycate. This should be available on the market and reimbursed for all patients. Better collaboration of medical societies with patients' associations may lead to increased number of diagnosed patients and improved management of mastocytosis.

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REFERENCES

1. **Arock M., Valent P.** Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives Expert Rev Hematol 2010; 3:497-516.
2. **Castells M., Austen K.F.** Mastocytosis: mediator-related sygns and symptoms. **Int Arch Allergy Immunol,** 2002; 127:147-52.
3. **Delsignore J.L., Dvoretsky P.M., Hicks D.G., O'Keefe R.J., Rosier R.N.** Mastocytosis presenting as a skeletal disorder. *Iowa Orthop J.* 1996; 16: 126-34.
4. **Edwards A.M., Hagberg H.** Oral and inhaled sodium cromoglicate in the management of systemic mastocytosis: a case report. Journal of medical case reports. 2010; 4:193
5. **Ellis J.M.** Urticaria pigmentosa. A report of a case with autopsy. *AMA Arch Pathol,* 1949; 48:426-9.
6. European Commission Report to European Parliament, European Committee, Economic and Social Committee and Regional Committee, COM 2014,548 final
7. European Medicines Agency. Public summary of opinion on orphan designation, EMA/COMP/439251/2013. Committee for Orphan Medicinal Products.
8. **Escribano L., Akin C., Castells M., Orfao A., Metcalfe D.D.** Mastocytosis: current concepts in diagnosis and treatment. *Ann Hematol,* 2002; 81:677-690.
9. **Lennert K., Parwaresch M.R.** Mast cells and mast cell neoplasia: a review. *Histopathology,* 1979; 3: 349-65.
10. **Longley B.J., Tyrrell L., Lu S.Z., Ma Y.S., Langley K., Ding T.G., Duffy T., Jacobs P., Tang L.H., Modlin I.** Somatic c-kit activating mutation in urticaria pigmentosa and aggressive mastocytosi: establishment of clonality in a human mast cell neoplasm. *Nat Genet*. 1996; 12: 312-4.
11. **Metcalfe D.D.** Classification and diagnosis of mastocytosis : current status. *J Invest Dermatol,*1991; 96: 2S-4S.
12. **Pardanani A.** How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage). *Blood,* 2013, Vol.121, no.16 : 3085-3094
13. **Sperr W.R., Valent P.** Diagnosis, progression patterns and prognostication in mastocytosis. *Expert Rev Hematol* 2012; 5: 261-274.
14. **Valent P., Aberer E., Beham-Schmid C., Fellinger C., Fucs W., Gleixner K.V., Greul R. et al.** Guidelines and diagnostic algorithm for patients with suspected systemic mastocytosis : a proposal of the Austrian competence network (AUCNM). *Am J, Blood, Res* 2013; 3(2):174-180.
15. **Valent P., Arock M., Bonadonna P., Brockow K., Broesby-Olsen S., Escribano L., Gleixner K.V. et al.** European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update and future perspectives. The Central European Journal of Medicine, 2012; 124: 807-814.
16. **Valent P., Horny H.P., Escribano L., Longley B.J., Li C.Y., Schwartz L.B., Marone G. et al.** Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res 2001;* 25:603-625.
17. **Valent P., Escribano L., Broesby-Olsen S., Hartmann K., Grattan C. et al.** Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy* 69 (2014); 1267-1274.
18. The European Competence Network on Mastocytosis – ECNM 2006: homepage on web-link : http:/www.ecnm.net (Access 2012).
19. The Mastocytosis Society (TMS). Mast Cell Disorders, Atlanta, USA, www.tmsforacure.org