

Anaphylaxis as a Manifestation of Systemic Mastocytosis: A Case Report and Review of Literature

Elie Haddad^{1,2*}, Carmen Joukhadar¹, Nabil Chehata¹ and Roy Nasnas^{1,3}

¹Infectious Diseases Department, Saint-Joseph University, Hotel Dieu de France Hospital, Medical Sciences and Nursing Campus, Lebanon

²Department of Infectious Disease, Pitie Salpetriere Hospital, France

³Infectious Diseases Department, Hotel Dieu de France Hospital, Lebanon

Abstract

Introduction: Anaphylaxis is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death”. The determination of different mast cells (MC) mediators, such as serum and/or plasma histamine and tryptase, is proposed for the diagnosis of anaphylaxis. There are differences in the clinical presentation of anaphylaxis in patients with indolent systemic mastocytosis versus idiopathic anaphylaxis.

Case presentation: This is the case of a 72-year-old female patient presenting with acute bacterial pyelonephritis treated with intra venous antibiotics. She developed a facial flush then a diffuse flush with hypoxia and respiratory arrest. The patient recovered with non-invasive ventilation without the need for intubation. A full blood panel returned normal and two bone marrows biopsies were performed. The second one showed the presence of a perivascular infiltrate mast cell, consistent with systemic mastocytosis.

Discussion: All aspects of systemic mastocytosis including the classification and the main clinical manifestations as well as the diagnosis were concisely reviewed. Then supportive and immunomodulator treatment were differentiated.

Conclusion: Patients suffering of systemic mastocytosis typically present anaphylactic symptoms primarily involving the cardiovascular system in the absence of urticaria and/or angioedema, which makes such clinical presentation highly suspicious. Patients suffering of c-MCD (Cutaneous-mast cell disease) need assistance in identifying their triggers and education on proper avoidance.

Keywords: Systemic mastocytosis; Anaphylaxis; Supportive treatment; Immunomodulator treatment; Flush

Introduction

Anaphylaxis is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death” [1]. Following the World Allergy Organization (WAO) criteria [2], the diagnosis of anaphylaxis is primarily based on clinical findings obtained through a detailed anamnesis and the recognition of the symptoms and signs present minutes to few hours after exposure to a known (or most likely) allergen or trigger for the patient. Typically, symptoms occur in ≥ 2 body systems mostly including skin and mucosa, the upper and lower respiratory tract, the gastrointestinal tract, the cardiovascular system, and/or the central nervous system [3]. Usually a combination of two or more of these clinical manifestations is observed. Although in some circumstances, anaphylaxis is also diagnosed when only one body system is clinically involved, e.g., reduced blood pressure observed few minutes to several hours after exposure to a trigger for the patient and generalized urticaria with a sudden onset after allergen immunotherapy as the only initial manifestation [4]. The determination of different mast cells (MC) mediators, such as serum and/or plasma histamine and tryptase, is proposed for the diagnosis of anaphylaxis [2,5]. There are differences in the clinical presentation of anaphylaxis in patients with indolent systemic mastocytosis versus idiopathic anaphylaxis [4,6].

Case Report

We present the case of a 72-year-old female patient with a history of dyslipidemia, diabetes presenting for acute pyelonephritis with high fever and chills for two days. She was put on non-steroidal anti-inflammatory drugs (NSAIDs) and sulfamethoxazole and trimethoprim twice daily for ten days at home with no relief of her urinary symptoms

after 24 hours. Urine culture was not performed. She was also complaining of fatigue since one month.

Two days after starting the treatment, she was admitted to the hospital for high fever, tachycardia, hypotension chills and urinary symptoms. She was put on IV carbapenem (imipenem and cilastatin) 500 mg intra venous (IV) 4 times per day. Her blood tests showed hemoglobin of 11.4g/l (normal range between 13 and 15) with normal white blood cells at 9600/mm³ and low platelets count (104000/mm³ with a normal range between 150000 and 400000). Creatinine and liver function tests were normal. The urine culture was positive with more than 1000000 colonies of *Escherichia coli* sensitive, resistant only to sulfamethoxazole and trimethoprim. All drawn blood cultures returned sterile. She was then switched to ofloxacin 200 mg IV 2 times per day.

The anemia and thrombocytopenia were attributed to the sepsis. After the initiation of IV treatment, fever has resolved and the urinary symptoms have disappeared. During her hospital stay, she presented a body flush at 96 hours with hypoxia that were attributed to the quinolones. She was put on IV ceftriaxone 2 g once daily with rapid

***Corresponding author:** Elie Haddad, Infectious Diseases Department, Faculty of Medicine, Saint-Joseph University, Hotel Dieu de France Hospital, Medical Sciences and Nursing Campus, Damascus Street, B.P. 11-5076, Riad El Solh, Beirut 1107-2180, Lebanon, Tel: 009613561121; E-mail: ehaddad@live.com

Received December 03, 2016; **Accepted** February 21, 2017; **Published** February 26, 2017

Citation: Haddad E, Joukhadar C, Chehata N, Nasnas R (2017) Anaphylaxis as a Manifestation of Systemic Mastocytosis: A Case Report and Review of Literature. J Clin Case Rep 7: 930. doi: [10.4172/2165-7920.1000930](https://doi.org/10.4172/2165-7920.1000930)

Copyright: © 2017 Haddad E, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

resolution of her flush. Two days later, the patient presented a severe hypoxia with a diffuse flush leading to respiratory arrest. She was transferred to the intensive care unit where she recovered with non-invasive ventilation without the necessity of an intubation.

A thoraco-abdomino-pelvic angioscan was performed to rule out pulmonary embolism and abscesses. It showed a moderate diffuse hepatosplenomegaly with few hepatic hilum lymph nodes reaching 1.3 cm in greatest diameter, few millimeter mesenteric lymph nodes, multiple diffuse low dense infracentimetric images in the spleen and two nodular low dense images of the upper pole of the left kidney corresponding to outbreaks of pyelonephritis.

In front of her rash, hypoxia, hypertension and respiratory arrest, we performed several blood tests to rule out pheochromocytoma and carcinoid tumor. She had a metanephrine and vanillylmandelic acid dosage 3 times and returned normal. The Urinary 5-hydroxyindoleacetic acid was in normal range. An immunoelectrophoresis of the protein was performed and returned normal. A chromogranine A dosage returned normal (98 ng/ml).

Therefore, we decided to perform more invasive tests.

A first bone marrow was performed to investigate the cause of her anemia and thrombocytopenia and returned normal. She had a gastroscopy and a colonoscopy for the anemia that showed a moderate gastritis. The anatomo-pathology result showed a few mast cells. In front of the presence of the MC and the clinical presentation, the diagnosis of systemic mastocytosis was of high suspicion. So a second bone marrow was performed that showed the presence of a perivascular infiltrate mast cell, consistent with systemic mastocytosis. The diagnosis of systemic mastocytosis was retained and the patient was put on IFN-alpha. After one and a half year, the patient is still free of any sign of recurrent anaphylaxis. She is not complaining of any skin lesions neither from fatigue.

Discussion

Mast cells are a crucial structural and functional component of the immune system; they play a key role in inflammatory reactions in allergic and nonallergic process [7,8]. Mastocytosis results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal MC that accumulate in one or more organ systems [9] more frequently the dermis, gastrointestinal tract, and cardiovascular system, frequently accompanied by neurologic complaints [6]. Patients with mastocytosis have symptoms due to the release of MC mediators, the infiltration of tissues by MC, or both [3].

The World Health Organization (WHO) defines seven categories of mastocytosis: (1) cutaneous mastocytosis (CM, when limited to the skin), (2) extracutaneous mastocytosis (ECM), (3) Idiopathic MS (IMS), (4) aggressive systemic mastocytosis (ASM), (5) SM associated with other clonal hematological non-MC lineage diseases (SM-AHNMD), (6) MC leukemia (MCL), and (7) MC sarcoma [10]. In addition, two other subvariants of indolent forms of the disease have been recognized: well-differentiated SM (WDSM) [11,12] and ISMs [13,14].

The clinical presentation of mastocytosis is heterogeneous, ranging from skin-limited disease (CM), particularly in pediatric cases where the majority have disease-onset within the first 2 years of life and commonly experience spontaneous regression of skin lesions, to a more aggressive variant with extra-cutaneous involvement (SM) that may be associated with multiple organ dysfunction/failure and shortened survival, that is generally seen in adult patients [9]. However, the diagnosis remains challenging to establish, as mastocytosis is relatively uncommon and

many clinicians are not readily accustomed to diagnosing and treating SM [15].

Physiopathology

Mastocytosis is frequently associated with somatic gain of function point mutations within KIT. KIT (CD117) is a Type III receptor tyrosine kinase that is expressed by MC, hematopoietic progenitor cells, germ cells, melanocytes and interstitial cells of Cajal in the gastrointestinal tract and is therefore functionally relevant for normal MC development, hematopoiesis, gametogenesis, melanogenesis, and regulation of slow gastric waves [16]. Overall, uncontrolled activation of the KIT receptor leads to increased production of MC and the accumulation of MC in extracutaneous organs, which can result in organ failure and even early death [15].

Diagnosis and Classification

The diagnosis and classification of mastocytosis is based on identification of neoplastic MC by morphological, immunophenotypic, and/or genetic (molecular) criteria [9]. The coexistence of one major criterion (presence of multifocal dense aggregates of ≥ 15 MC in bone marrow (BM) and/or other extracutaneous tissues) plus one minor criterion or simultaneous detection of ≥ 3 of the following minor diagnostic criteria: (1) identification of morphologically atypical MC in smears or biopsy sections of BM or other extracutaneous organs, (2) aberrant expression of CD25 and/or CD2 by BMCMC, (3) detection of the D816V KIT mutation in BM, blood, or other extracutaneous organs, and (4) sBT $20 \geq \mu\text{g/L}$ in the absence of other disorders associated with increased serum tryptase [17].

It must be emphasized however that neither tryptase nor KIT/CD117 immunostaining is able to distinguish between normal and neoplastic MC [9].

A serum tryptase level should be obtained several weeks after any anaphylactic reaction has resolved, so as not to confuse reactive MC activation with constitutive production of tryptase by MCs. Elevations above 20 ng/mL in suspected patients often yields a diagnosis of SM upon full investigation [15].

Neoplastic MC generally express CD25 and/or CD2, and the abnormal expression of at least one of these two antigens counts as a minor criterion toward the diagnosis of SM per the WHO system [18].

The two largest series of mastocytosis patients reported so far support the notion that the prevalence of IgE-mediated allergy among patients with mastocytosis is similar to that observed for the general population [19]. In both series, the majority of the anaphylactic episodes in mastocytosis were classified as idiopathic, non-IgE mediated, and/or triggered by hymenoptera sting, as also described by others [14,20].

The mean frequency of MC mediator-related symptoms reported in mastocytosis in association with NSAIDs is of around 14%, ranging from 8% to 11% if restricted to the frequency of anaphylaxis [3].

The most frequently observed anaphylactic symptoms involves the cardiovascular system, e.g., presyncope, tachycardia, hypotension, shock, cardiac arrest [3].

Organs Biopsies

Biopsy of organs other than BM, such as liver or spleen, is infrequently pursued, either for diagnostic purposes or to demonstrate MC infiltration as the cause of impaired organ dysfunction [9]. The diagnosis of SM in the absence of skin involvement is considerably more

challenging, particularly in those patients with an indolent SM variant with low mast cell burden, termed isolated bone marrow mastocytosis (BMM); consequently, a high index of suspicion is required in the setting of recurrent unexplained anaphylaxis, flushing, osteoporosis, gastrointestinal ulcerative disease, or chronic abdominal cramping [9].

Bone Marrow Histology

The current diagnostic approach for SM starts with a BM examination since this site is almost universally involved in adult mastocytosis, and histological diagnostic criteria for non-BM, extracutaneous organ involvement in SM have not been firmly established or widely accepted yet [9].

Clinical manifestations

Clinically, symptoms depend on the subtype of SM and are due to MC mediator release and/or organ infiltration [15]. Skin manifestations are the hallmark of CM but also are a common manifestation of SM, especially ISM. There are reddish-brown raised papules or plaques and are indicative of systemic disease in 10% to 70% of cases of SM [21]. MC accumulation in the dermis can spontaneously result in the release of MC mediators leading to flushing, pruritus, and urticaria [21]. Acute release of MC mediators also renders patients with SM at increased risk of anaphylaxis [19].

Fatigue is the most common symptom of SM, but other constitutional symptoms such as weight loss, anorexia, night sweats, and fevers can be presenting symptom due to cytokines secretions [15]. Increased MC mediator release also can have effects on the musculoskeletal system, with 31% of SM patients experiencing symptomatology that can resemble fibromyalgia [22]. Extracutaneous MC infiltration is the hallmark of SM. Commonly affected organs are bone marrow, liver, lymph nodes, gastrointestinal tract, and spleen. Hematologic abnormalities are common. Anemia is present in up to half of patients with SM. Thrombocytopenia and leukocytosis is also common. Eosinophilia can also be observed in approximately 15% of patients [23].

Treatment

Therapy will primarily consist of avoidance of these triggers and mast cell stabilizing agents [6].

Supportive treatment

In case of anaphylaxis, (1) remove the trigger if possible; (2) assess the patient's circulation, airway, breathing, mental status, and skin; (3) simultaneously, call for help and (self) inject epinephrine intramuscularly in the mid-antrolateral thigh; and (4) place the patient on the back (or in a position of comfort if there is respiratory distress and/or vomiting), with the lower extremities elevated. Supplemental oxygen should be administered, an intravenous catheter should be inserted and intravenous fluid resuscitation given, cardiopulmonary resuscitation initiated, and the patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation monitored; an electrocardiogram should be performed and continuous noninvasive monitoring. Second-line medications such as H1 and H2 antihistamines, as well as corticosteroids, are also recommended in c-MCD [24].

Immunomodulator treatments

In general, treatment with small-molecule kinase inhibitors has yielded only modest clinical benefits, likely due to yet unrecognized

complexities in the molecular pathogenesis of SM, redundancies in cellular signaling pathways and/or ineffectiveness of currently available *in vivo* KITD816V-inhibitors [9]. Current therapy in WHO-defined SM is largely palliative and directed at MC degranulation symptoms (e.g., pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks), symptomatic skin disease (e.g., urticaria pigmentosa) and/or organ dysfunction from MC tissue infiltration (e.g. hypersplenism or pathologic fracture) [9]. Different drugs (alone or in distinct combinations) are indicated [24,25]: (1) oral disodium cromolyn MC-stabilizer; (2) scheduled or at demand sedating H1 antihistamines (dexchlorpheniramine); (3) scheduled or at demand non-sedating H1 antihistamines, combined with a sedating antihistamine in highly symptomatic cases; (4) scheduled H2 antihistamines; (5) scheduled leukotriene antagonists; and (6) corticosteroids for uncontrolled MC mediator-related symptoms. In stress induced anaphylaxis, a psychiatric workup followed by an adequate anxiolytic and/or antidepressant therapy is recommended [3].

IFN- α is often considered the first line cytoreductive therapy in symptomatic SM; since the initial report in 1992, several case reports or small series have shown IFN- α (IFN- α 2b in most instances) to improve symptoms of MC degranulation, decrease bone marrow MC infiltration, and ameliorate mastocytosis-related ascites/hepatosplenomegaly, cytopenias, skin findings and osteoporosis [9].

The time to best response may be a year or longer [26] and delayed responses to therapy have been described [9]. The adverse effects include flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism [9].

The starting dose is 1–3 million units (MU) subcutaneously three times per week, followed by gradual escalation to 3–5 MU three to five times per week, if tolerated. Prednisone (30–60 mg day⁻¹) is commonly added at the start of treatment to improve tolerability and response, and is tapered over a 2 to 3-month period. IFN- α treatment is generally continued as long as a response is observed and there are no intolerable adverse effects [9].

The 2-chlorodeoxyadenosine (cladribine or 2-CdA) has demonstrated *in vitro* and *in vivo* activity against neoplastic MC; the published experience suggests that 2-CdA has therapeutic activity in all SM subtypes including in MCL.

Imatinib mesylate (IM) demonstrates *in vitro* efficacy against wild-type KIT and certain trans-membrane (F522C) and juxta-membrane (V560G) KIT mutants, but not the common kinase (D816V) domain mutants [9].

Hydroxyurea (HU): The dose ranged from 500 mg every other day to 2000 mg day⁻¹. Treatment response was evaluable in 26 patients; control of thrombocytosis, leukocytosis, and/or hepatosplenomegaly was observed in 5 SM-AHNMD patients [9].

These therapies include humanized murine monoclonal antibody omalizumab and tyrosine kinase inhibitors.

Conclusion

Mast cell activation syndrome is a very complicated disorder that can present with common and unusual symptoms in multiple organ systems. The diagnosis is often not simple. These patients typically present anaphylactic symptoms primarily involving the cardiovascular system in the absence of urticaria and/or angioedema, which makes such clinical presentation highly suspicious. Patients suffering with

c-MCD need assistance in identifying their triggers and education on proper avoidance. Therapy will primarily consist of avoidance of these triggers and mast cell stabilizing agents.

References

1. Simons FER, World Allergy Organization (2010) World Allergy Organization survey on global availability of essentials for the assessment and management of anaphylaxis by allergy-immunology specialists in health care settings. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 104: 405-412.
2. Simons FER, Arduzzo LRF, Bilo MB, El-Gamal YM, Ledford DK, et al. (2010) World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 127: 587-593.
3. Matito A, Alvarez-Twose I, Morgado JM, Sanchez-Munoz L, Orfao A, et al. (2014) Anaphylaxis as a clinical manifestation of clonal mast cell disorders. *Curr Allergy Asthma Rep* 14: 450.
4. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G (2010) Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 125: 569-574.
5. Caughey GH (2006) Tryptase genetics and anaphylaxis. *J Allergy Clin Immunol* 117: 1411-1414.
6. Frieri M, Patel R, Celestin J, Curr J (2013) Mast cell activation syndrome: a review. *Curr Allergy Asthma Rep* 13: 27-32.
7. Fukuoka Y, Xia H-Z, Sanchez-Munoz LB, Dellinger AL, Escribano L, et al. (2008) Generation of anaphylatoxins by human beta-tryptase from C3, C4, and C5. *J Immunol* 180: 6307-6316.
8. Nunez-Lopez R, Escribano L, Scherthaner G-H, Prados A, Rodriguez-Gonzalez R, et al. (2003) Overexpression of complement receptors and related antigens on the surface of bone marrow mast cells in patients with systemic mastocytosis. *Br J Haematol* 120: 257-265.
9. Pardanani A (2013) Systemic mastocytosis in adults: 2013 update on diagnosis, risk stratification, and management. *Am J Hematol* 88: 612-624.
10. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, et al. (2007) Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 37: 435-453.
11. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, et al. (2006) KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood* 108: 2366-2372.
12. Teodosio C, Garcia-Montero AC, Jara-Acevedo M, Sánchez-Munoz L, Alvarez-Twose I, et al. (2010) Mast cells from different molecular and prognostic subtypes of systemic mastocytosis display distinct immunophenotypes. *J Allergy Clin Immunol* 125: 719-726.
13. Florian S, Krauth M-T, Simonitsch-Klupp I, Sperr WR, Fritsche-Polanz R, et al. (2005) Indolent systemic mastocytosis with elevated serum tryptase, absence of skin lesions, and recurrent severe anaphylactoid episodes. *Int Arch Allergy Immunol* 136: 273-280.
14. Alvarez-Twose I, Gonzalez de Olano D, Sánchez-Munoz L, Matito A, Esteban-Lopez MI, et al. (2010) Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 125: 1269-1278.
15. Tremblay D, Carreau N, Kremianskaya M, Mascarenhas J (2015) Systemic Mastocytosis: Clinical Update and Future Directions. *Clin Lymphoma Myeloma Leuk* 15: 728-738.
16. Miettinen M, Lasota J (2005) KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. *Appl Immunohistochem Mol Morphol AIMM Off Publ Soc Appl Immunohistochem* 13: 205-220.
17. Valent P, Agis H, Sperr W, Sillaber C, Horny H-P (2008) Diagnostic and prognostic value of new biochemical and immunohistochemical parameters in chronic myeloid leukemia. *Leuk Lymphoma* 49: 635-638.
18. Horny HP, Metcalfe DD, Bennett JM (2008) Mastocytosis. In: Swerdlow SH, Campo E, Harris NL (eds). *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. Lyon: International Agency for Research and Cancer (IARC) pp 54-63.
19. Brockow K, Jofer C, Behrendt H, Ring J (2008) Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 63: 226-232.
20. Alvarez-Twose I, Zanotti R, González-de-Olano D, Bonadonna P4, Vega A, et al. (2014) Nonaggressive systemic mastocytosis (SM) without skin lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM. *J Allergy Clin Immunol* 133: 520-528.
21. Soter NA (2000) Mastocytosis and the skin. *Hematol Oncol Clin North Am* 14: 537-555.
22. Valent P, Sotlar K, Sperr WR, Escribano L4, Yavuz S, et al. (2014) Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. *Ann Oncol Off J Eur Soc Med Oncol ESMO* 25: 1691-1700.
23. Escribano L, Akin C, Castells M, Schwartz LB (2006) Current options in the treatment of mast cell mediator-related symptoms in mastocytosis. *Inflamm Allergy Drug Targets* 5: 61-77.
24. Hauswirth AW, Simonitsch-Klupp I, Uffmann M, Koller E, Sperr WR, et al. (2004) Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. *Leuk Res* 28: 249-257.
25. Böhm A, Sonneck K, Gleixner KV, Schuch K, Pickl WF, et al. (2010) In vitro and in vivo growth-inhibitory effects of cladribine on neoplastic mast cells exhibiting the imatinib-resistant KIT mutation D816V. *Exp Hematol* 38: 744-755.
26. Patel R, Celestin J, Frieri M (2012) An unusual case of mast cell activation syndrome. *J Allergy Clin Immunol* 129: 475.