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Title

Vaccination Management In Children and Adults With Mastocytosis

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Research letter

To the Editor:

Mastocytosis includes a heterogeneous group of disorders characterized by the presence of clonal mast cells (MC) in cutaneous tissues and extracutaneous organs [1,2]. The disease presents in two primary age-related patterns, which may differ in their clinical manifestations and prognosis [1,2]. Pediatric-onset mastocytosis usually consists of cutaneous disease and tends to resolve itself by adolescence in most cases, in contrast to adult-onset mastocytosis which has a normal chronic course [2]. Moreover, the outcome of mastocytosis in childhood-onset forms is influenced by the morphology of the cutaneous manifestations and those cases with maculopapular cutaneous mastocytosis-large lesions have a more favorable prognosis [3].

Patients with mastocytosis are at risk of anaphylaxis with hymenoptera venom (HV), drugs including those administered for general anesthesia and food as principal causes [4,5]. Idiopathic anaphylaxis is the most frequent presentation in children [4]. However, the risk of anaphylactic reactions is lower in children and correlates with severity of skin involvement and serum tryptase (sT) levels [2].

Stimuli that can trigger activation of mast cells and mediator release includes various factors, such as physical, chemical, emotional and unspecific ones [6]. Vaccination is considered, together with fever, a possible trigger of mediator release in subjects with mastocytosis, particularly in children [1,4]. Moreover, there are also some substances such as dextran, gelatine and polymyxin B that can be present in some vaccines that may be possible triggers [6]. Sporadic cases of cutaneous manifestations of mastocytosis after vaccination in children have been published [4,5,7,8]; moreover, an Italian study of 72 children with mastocytosis demonstrated a moderate risk of immediate and non-immediate reactions associated with the first dose of hexavalent vaccine [6%] [9]. However, epidemiological data regarding the safety of vaccines in subjects with mastocytosis are lacking.

Patients and methods

We collected clinical and vaccination records of paediatric and adult patients with cutaneous and/or systemic mastocytosis referred to the National Multidisciplinary Outpatient Clinics for Mastocytosis (Haematology, Dermatology, Allergy and Immunology Units) at the Verona University Hospital in the period 2010-2011. Diagnosis of mastocytosis was established according to the 2016 revision of the WHO classification. The following data were analyzed: age, sex, age of onset of disease and diagnosis, mediator-related symptoms and in particular episodes of anaphylaxis, serum basal tryptase levels (bT) with reference range $< 11.4 \mu\text{g/L}$ as established by the manufacturer (ImmunoCAP Tryptase, ThermoFisher Scientific, Uppsala, Sweden), bone marrow study and skin biopsy results. A specific form was created by vaccination consultants at the Green Channel immunization clinic [10] to collect information regarding vaccines administered before and after the diagnosis of mastocytosis, description of any reaction to vaccines and its treatment, and previous episodes of anaphylaxis to any substances. The vaccines administered to children are established by the Italian pediatric vaccination schedule: combined diphtheria, tetanus, pertussis, polio, hepatitis B; *Haemophilus influenzae* b, pneumococcal and meningococcal conjugated vaccines, measles, mumps, rubella (MMR) and varicella vaccines; influenza, tetanus boosters and vaccines for international travellers were also recorded. The vaccination form was filled in by specialists during periodic dermatological, haematological and/or allergological evaluations of patients and their personal vaccination records were collected.

Informed consent of personal data management with respect to privacy rights was obtained from patients or their parents.

Results and discussion

A total of 102 patients' records were evaluated, including 35 children up to 18 years of age and 67 adults. Demographic data of the study population are reported in Table S1 in the Online Repository. The diagnosis was distributed as follows: 63 out of 67 adult patients had indolent systemic mastocytosis (ISM), while 27 of them presented skin lesions (ISMs+), 1 aggressive systemic mastocytosis (ASM), 2 maculo-papular cutaneous mastocytosis (MPCM) and 1 mastocytosis in the skin (MIS); 26 out of 35 children were affected by MPCM, 6 by mastocytoma and 3 by diffuse cutaneous mastocytosis (DCM). Forty-seven subjects (46%) had experienced previous episodes of anaphylaxis to the following triggers: HV: 36, drugs: 4, insect bite: 2, drugs and HV: 2, food: 1, food and HV: 1; the trigger was unknown in one subject. Increased bT levels were present in 63/96 (66%) subjects. There were 18 children and 5 adults on anti-histamine therapy.

Seventy-two patients (71%) documented one or more vaccine administrations after the onset of mastocytosis and 65 of them (90%) did not report any adverse event. Vaccines were administered at the local Public Health Unit in the majority of subjects; only in 3 children was vaccination performed in a hospital setting as recommended by the attending dermatologist. In particular, 30 children and 42 adults received a total of 137 vaccine doses (Table 1). All adults tolerated the vaccines without adverse events. No premedication was prescribed before vaccination.

Seven children (23% of vaccinated children) manifested post-vaccination reactions (Table 2). In particular, clear cutaneous signs and symptoms due to mast cell mediator release occurred in 4 children (13%) and two of them tolerated subsequent vaccinations without reactions; unspecific reactions with fever were reported in 2 cases, while one child had fever and diarrhoea 24 hours after meningococcal vaccine administration. The reactions were self-limiting and patients recovered after symptomatic treatment. No episodes of anaphylaxis to vaccines were reported (Table 2).

Our study provides data on the outcome of vaccination, which is considered a potential trigger of MC mediator release, in children and adults with mastocytosis. Epidemiological data on frequency and severity of mastocytosis-related signs and symptoms after exposure to some triggering factors have been published [4-6], but studies specifically addressing vaccination are lacking. Vaccines, together with fever, are considered unspecific triggers of MC degranulation; in fact, the few cases of reactions to vaccines reported in the literature were not associated with defined vaccine components [5,7-8].

Our data show that vaccination was tolerated without reactions by adults with mastocytosis, whereas 4 children had manifestations of MC degranulation after immunization. Interestingly, among the cases who reacted to the vaccination stimulus, 2 children had solitary mastocytoma, one had MIS and only one suffered from a diffuse form of mastocytosis that has an increased risk of reactions, although this boy manifested the same delayed cutaneous reaction both after the first and the second administration. Differently, another 2 children with DCM did not show any adverse events. One child had fever and diarrhoea 24 hours after meningococcal vaccine administration: although diarrhoea can be a consequence of MC degranulation, in this case the reaction was judged to be probably unrelated to mastocytosis due to the long time interval and also because this event is reported as "frequent" in the package insert of the meningococcal C vaccine administered.

We could not find any relationship between types of vaccines administered (i.e. live or inactivated, combined, conjugated, toxoids, etc,) and risk of manifesting MC degranulation symptoms after immunization. Moreover, two children who reacted to vaccination subsequently tolerated the same vaccine components, one of whom received the hexavalent formulation, thus confirming the unspecific nature of the reaction. In regard to bT levels, this marker did not show any predictive value in our study population, as it was below the cut-off level in all cases who presented reactions to vaccines (Table S1). Vaccine adverse reactions possibly involving mast cell degranulation may also occur in subjects without mastocytosis: in our region the rate of vaccine-related cutaneous

manifestations with onset within 12 hours after administration reported to the regional surveillance system for vaccine adverse events named the Green Channel [10] is 2.3/100,000 doses when considering all administered vaccines, but it rises to 11.3/100,000 after the combined hexavalent vaccine, 9.62 after pneumococcal conjugated and 8.15 after HPV. Therefore, these vaccines can be responsible for an increased, although low, risk of skin manifestations in children without clear risk factors. However, in children with mastocytosis the risk for these reactions is increased (13% per child and 5% per administered dose).

Although patients with mastocytosis can be vaccinated according to the standard schedule, precautions to prevent MC activation and degranulation have been formulated by experts, particularly in cases of diffuse skin manifestations [7]. According to their recommendations, vaccination should be performed under observation with medications available to treat anaphylaxis [5]. Protocols for premedication with steroids, antihistamines and leukotriene receptor antagonists or cromolyn therapy and single injection regimens have been applied to prevent complications [7], but official guidelines have not been released.

On the basis of these findings, the overall safety of vaccination in patients with mastocytosis is confirmed. In a few cases reactions were observed, particularly in children. Taking into account our procedures for vaccine administration defined by the Public Health Authority, together with the specialized regional Green Channel consultation clinic for this area [10], we recommend, as a precaution, prolonging the observation period of the vaccinee in the waiting room, which is routinely established at 15 minutes, to at least 30 minutes after vaccination for subjects with mastocytosis. In addition parents are trained in the surveillance of the vaccinated child for early recognition of manifestations and their management, including the use of an epinephrine autoinjector where necessary. Single injections of vaccines are usually recommended by our regional immunization centre in case of previous vaccine-related reactions, both in subjects with or without mastocytosis [10]. In the case of children with mastocytosis, avoidance of co-administration of

multiple vaccines is specifically indicated. Premedication is not recommended by our group, but it may be useful in selected cases.

In the Veneto region, standard anaphylaxis treatment is available at Vaccination Units to provide necessary safety, particularly for subjects at risk of immediate reactions.

Further in-depth studies on vaccination in subjects with mastocytosis are needed to provide official recommendations on this topic.

Conflicts of Interest

The authors declare to have no conflicts of interest.

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Authors contributions

GZ and PB conceived the idea, with input from RZ. All authors recruited and managed patients with mastocytosis and collected data on vaccinations. RZ, RO and PB advised on the preparation of the manuscript. GZ wrote the article.

References

1. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children. *Am J Clin Dermatol* 2011; 12(4):259-70.
2. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol*. 2016 Jan;137(1):35-45.
3. Wiechers T, Rabenhorst A, Schick T, Preussner LM, Förster A, Valent P, Horny HP, Sotlar K, Hartmann K. Large maculopapular cutaneous lesions are associated with favorable outcome in childhood-onset mastocytosis. *J Allergy Clin Immunol*. 2015;136(6):1581-90
4. Matito A. & Carter M. Cutaneous and Systemic Mastocytosis in Children: A Risk Factor for Anaphylaxis? *Curr Allergy Asthma Rep* (2015) 15 (5): 22-30.
5. Brockow K, Jofer C, Behrendt H, Ring J Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008 Feb;63(2):226-32.
6. Escribano L, Akin C, Castells M, Orfao A, Metcalfe DD. Mastocytosis: current concepts in diagnosis and treatment. *Ann Hematol* 2002; 81:677-90.
7. Bankova LG, Walter JE, Iyengar SR, Lorenzo ME, Hornick JL, Castells MC. Generalized bullous eruption after routine vaccination in a child with diffuse cutaneous mastocytosis. *J Allergy Clin Immunol: In practice* 2013; 1:94-6
8. Poulton JK, Kauffman CL, Lutz LL, Sina B. Solitary mastocytoma arising at a hepatitis B vaccination site. *Cutis* 1999; 63(1): 37-40.
9. Parente R, Pucino V, Magliacane D, Petraroli A, Loffredo S, Marone G, Triggiani M. Evaluation of vaccination safety in children with mastocytosis. *Pediatr Allergy Immunol* Sep 3. doi: 10.1111/pai.12647.
- 10 Micheletti F, Peroni D, Piacentini G, Schweiger V, Mirandola R, Chiesa E, Zanoni G. Vaccine

allergy evaluation and management at the specialized Green Channel Consultation Clinic. Clin
Exp Allergy. 2012 Jul;42(7):1088-96.

Table 1. Vaccines administered after diagnosis in patients with mastocytosis.

Vaccines	N. of doses in children	N. of doses in adults	N. of reactions* (%)
Diphtheria-Tetanus-acellular Pertussis (DTaP)	3	5	-
Diphtheria	2	-	-
Diphtheria-Tetanus	1	5	-
acellular Pertussis	4	-	-
Tetanus	5	15	-
Hexavalent °	11	-	4 (36)
Pneumococcal C	12	1	2 (15)
Meningococcal C	6	-	-
Inactivated Polio	4		-
Live attenuated Polio	1	1	-
Haemophilus Influenzae type b	2	-	-
Hepatitis A+B	-	1	-
Hepatitis B	4	4	-
Hepatitis A	1	1	-
Measles-Mumps-Rubella-Varicella	5	-	-
Measles-Mumps-Rubella (MMR)	10	2	-
Varicella	3		-
Human Papilloma Virus	2	1	1 (33)

Typhoid vaccine (oral)	1	1	-
Smallpox	2	-	-
Bacillus Calmette–Guérin	1	-	-
Yellow fever	-	1	-
Influenza	-	24	-
Total	80	57	

* all reactions attributable to mast cell degranulation in children

Hexavalent: diphtheria-tetanus toxoid-acellular pertussis-hepatitis B- inactivated polio vaccine-*Haemophilus influenzae b* vaccine;

°DTaP-IPV-Hib-HepB = diphtheria, tetanus, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b, hepatitis B vaccine.

Table 2. Personal and clinical data of patients with reactions to vaccines.

Pt no.	Sex / age (yrs)	Diagnosis / age at diagnosis (yrs)	Responsible vaccines (N. of the dose)	Symptoms	Time interval	Basal	
						tryptase level (ng/mL)	Follow-up of subsequent vaccinations
1	M/0.5	Mastocytoma/0.5	Hexavalent (1)	Immediate urticaria, angioedema	20 min	4.3	DTaP, IPV, HB, HiB, MMRV tolerated (in hospital)
2	F/0.6	Mastocytoma/0.4	Hexavalent (2)	Immediate facial, local flushing	20 min	n.d.	Hexavalent III dose tolerated (in hospital)
3*	F/11	MPCM/0.5	HPV (1)	Wheals on arm (same side of	12 h	4.5	-

				injection), nasal obstruction			
4	M/2	DCM/0.4	Hexavalent (1 and 2)+ PCV (1 and 2)	Wheals and pruritus on trunk, febrile convulsions	12 h	11	
5	F/6	Mastocytoma/2	MenC (1)	Fever, diarrhoea	24 h	4.6	PCV III dose tolerated
6	M/1	MPCM/0.2	PCV (2), MenC (1)	Fever	8 h	4.5	-
7	M/5	Mastocytoma/0.6	Hexavalent (3)	Injection site reaction, fever, crying	8 h	7.7	-

Pt: patient; yrs: years; M, Male; F, Female;

MPCM: maculo-papular cutaneous mastocytosis; DCM: diffuse cutaneous mastocytosis

* history of anaphylaxis to food (pork meat)

Hexavalent: diphtheria-tetanus toxoid-acellular pertussis-hepatitis B- inactivated polio vaccine-*Haemophilus influenzae b* vaccine; DTaP: diphtheria-tetanus toxoid-acellular pertussis vaccine; IPV: inactivated polio vaccine; HB: hepatitis B vaccine; HiB: *Haemophilus influenzae b* vaccine; MMRV: measles, mumps, rubella, varicella vaccine; PCV: pneumococcal vaccine; HPV: human papilloma virus vaccine; Men C: meningococcal C vaccine.