Hypersensitivity to drugs and mast cell disorders

Knut Brockow
Klinik und Poliklinik für Dermatologie und Allergologie, Technische Universität München
Case report

- 46-year old female patient
- Occurrence of facial swelling, dyspnea and tachycardia 3-4 h after intake of acetylsalicylic acid or ibuprofen in different episodes
- No known allergy, atopic diseases or other abnormality noted
What has this patient?
What has this patient?

- Minimal maculopapulous cutaneous mastozytosis
- Tryptase 10,5 kU/l
- In the bone marrow biopsy focal mast cell infiltrates, D816V mutation, CD25 expression of mast cells

→ ISM as underlying disease
Mastocytosis is a disease characterized by an abnormal increase in mast cells.

Cutaneous or systemic mastocytosis

Incidence: 13.0 per 100,000 inhabitants

Complications:

- Symptoms because of mast cell mediator release (anaphylactoid reactions, constitutional symptoms)
- Associated hematological diseases
  - Osteoporosis
# WHO criteria of systemic mastocytosis

## Main criterium *
- Dense multifocal mast cell infiltrates (≥ 15 cells) in bone marrow or other extracutaneous organ

## Minor criteria#
- >25% of extracutaneous mast cells are spindle shaped or have atypical morphology
- KIT mutation in codon 816 in tissue
- Mast cell expression of CD2 and/or CD25
- Total serum tryptase value basal > 20ng/ml

1x* or 3x # = systemic mastocytosis
Is immediate drug hypersensitivity common and severe in mastocytosis and patients with increased basal serum tryptase levels?
1. Anaphylaxis in patients with mastocytosis
Basis of anaphylaxis in mastocytosis

Mastocytosis → Activating KIT mutation →

- Hyperreactive mast cell phenotype
- Mast cell proliferation

Hyperreactive mast cell phenotype →

- Mast cell activation
- Trigger factors

Mast cell activation →

- Local symptoms
- Anaphylaxis
- Systemic symptoms

Anaphylaxis →

- More severe symptoms
- Higher number of effector mast cells
Anaphylaxis seldom in children
often in adults with mastocytosis

Anaphylaxis is more Common in SM

Brockow K et al. Allergy 2008; 63: 226-32
2. Trigger factors for anaphylaxis in adults with mastocytosis
Mastocytosis risk factor for severe anaphylaxis

Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to *Hymenoptera* stings

Dagmar Ludolph-Hauser, Franziska Ruëff, Claudia Fries, Pia Schöpf, Bernhard Przybilla

Anaphylactic IgE-mediated reactions to *Hymenoptera* stings vary in their severity for reasons that are not clear. We investigated patients with a history of systemic anaphylactic reactions to honeybee or wasp stings. Nine (75%) of 12 patients with raised tryptase concentrations but only 28 (28%) of 102 patients with lower tryptase concentrations, had a history of severe sting reactions (p=0.004). Raised baseline serum concentrations of mast-cell tryptase and mastocytosis are potential risk factors for severe allergic reactions to *Hymenoptera* venom.
Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: Importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity

Franziska Ruëff, MD, Bernhard Przybilla, MD, Maria Beatrice Biló, MD, Ulrich Müller, MD, Fabian Scheipl, Werner Aberer, MD, Joëlle Birnbaum, MD, Anna Bodzenta-Lukaszyk, MD, Floriano Bonifazi, MD, Christoph Bucher, MD, Paolo Campi, MD, Ulf Darsow, MD, Cornelia Egger, MD, Gabrielle Haeberli, MD, Thomas Hawranek, MD, Michael Körner, MD, Iwona Kucharewicz, MD, Helmut Küchenhoff, PhD, Roland Lang, PhD, Oliviero Quercia, MD, Norbert Reider, MD, Maurizio Severino, MD, Michael Sticherling, MD, Gunter Johannes Sturm, MD, and Brunello Wüthrich, MD

Munich, Hannover, and Erlangen, Germany, Ancona, Florence, and Faenza, Italy, Bern and Zurich, Switzerland, Graz, Innsbruck, and Salzburg, Austria, Marseille, France, and Bialystock, Poland

TABLE I. Frequency and classification of systemic reactions (n = 962) at the index field sting modified according to Ring and Meßmer

<table>
<thead>
<tr>
<th>Classification</th>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Generalized skin symptoms (eg, flush, generalized urticaria, angioedema)</td>
<td>15.2</td>
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<tr>
<td>Grade II</td>
<td>Mild-to-moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms</td>
<td>63.4</td>
</tr>
<tr>
<td>Grade III</td>
<td>Anaphylactic shock, loss of consciousness</td>
<td>21.0</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Cardiac arrest, apnea</td>
<td>0.4</td>
</tr>
</tbody>
</table>

![Graph showing baseline tryptase concentration (µg/l) vs. odds ratio]
Severity and perceived trigger factors

- Food
- Alcohol
- Hymenoptera stings
- Drugs
- Unidentified
- Exercise
- Posture change
- Food + alcohol
- Food + Alcohol + aspirin
- Food + exercise
- Exercise + hymen. sting
- Exercise + heat
- Exercise + heat + alcohol
- Mech. stimulus + heat

Number of reactions (n)

- Single elicitors
- Combination elicitors

Drug hypersensitivity in patients with mastocytosis in published studies

- Brockow K.  
  Allergy 2008; 63:226

  NSAIDs (n = 3)  
  Contrast media (n = 2),  
  Betalactams (n = 1)  
  - amoxicillin  
  Codeine (n = 1)  
  Local anaesthetic (n = 1)

- Gonzalez de Olano D.  
  CEA 2007, 37: 1547

  NSAIDs (n = 4)  
  Betalactams (n = 2)  
  - amoxicillin/clavulanic,  
  - ampicillin+aminoglycoside  
  Streptomycin (n = 1)  
  Phenylephrine (n = 1)  
  General anesthesia (n = 1)

Drugs eliciting anaphylaxis in patients with mastocytosis are those also eliciting hypersensitivity reactions in other populations
Acetylsalicyic acid and NSAIDs may lead to severe anaphylaxis
Morphins and cough suppressants containing codein may lead to anaphylaxis.
Sudden Intraoperative Hypotension in a Patient with Asymptomatic Urticaria Pigmentosa

Michael P. Hosking, MD, and Mark A. Warner, MD

CASE REPORT
Systemic mastocytosis presenting as profound cardiovascular collapse during anaesthesia

S. T. A. Vaughan¹ and G. N. Jones²

¹ Senior House Officer in Anaesthesia, and ² Consultant Anaesthetist, Royal Preston Hospital, Sharoe Green Lane, Preston PR2 4HT, UK
Increased risk to react in general anaesthesia has been assumed in patients with previously unrecognized mastocytosis.
3. Should NSAIDs, opioids and muscle relaxants be avoided in patients with mastocytosis?
Overall, out of 137 patients, only nine (6.6%) had a basal tryptase >11.4 ng/ml, and only two (1.5%) were diagnosed with mastocytosis.
European Network on Drug Allergy

• Allergists/immunologists/dermatologists from different European countries dedicated to drug allergy
  • EAACI interest group
  • Facilitate diagnosis and therapy in drug allergy
  • Publish test protocols
  • Multicenter studies

Madrid, October 2015
Pediatric Mastocytosis: Routine Anesthetic Management for a Complex Disease

Melody C. Carter, MD*
Ashraf Uzzaman, MD*
Linda M. Scott, CRNP*
Dean D. Metcalfe, MD*
Zenaide Quezado, MD†

BACKGROUND: Pediatric mastocytosis consists of a spectrum of clinical variants characterized by increased numbers of resident mast cells in various organ systems. Mast cells are instrumental in mediating anaphylaxis and patients with mastocytosis are at risk to develop provoked and unprovoked episodes of anaphylaxis.

METHODS: We examined perianesthetic records of patients with pediatric mastocytosis who were anesthetized for diagnostic and surgical procedures from 1993 to 2006. In addition, we conducted a literature review of the anesthetic experience in pediatric mastocytosis.

RESULTS: Twenty-two patients with pediatric mastocytosis, with a median age of 3.2 yr (range, 6 mo–20 yr) at the time of the procedure, were anesthetized for 29 diagnostic and surgical procedures. All variants of the disease are represented in this series. Most patients had a history of flushing, pruritus, gastro-esophageal reflux diseases, and abdominal pain; one patient had a history of spontaneous anaphylaxis. Routine anesthetic techniques were used and, despite the complexity of the disease, the perioperative courses were uncomplicated and without serious adverse events.

CONCLUSIONS: We reviewed the main features of pediatric mastocytosis, its anesthetic and perioperative implications, and describe a practical approach to the anesthetic management of pediatric patients with the disease. Although many drugs used routinely in anesthesia reportedly caused mast cell degranulation, deviations from routine anesthesia techniques are not necessarily warranted. However, an understanding of the anesthetic implications of the disease and meticulous preparation to treat possible adverse events are advised.

29 procedures in 22 children:

- anesthesia without premedication (but symptomatic therapy H1+H2 in 41%, cortison in 5%)
- Procedure as planned by anesthetist
- 24x general anesthesia, 7x intubation

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Table 4. Anesthetic Management of Patients with Pediatric Onset Mastocytosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Time</th>
<th>Anesthetic</th>
<th>Antibiotic</th>
<th>Procedure</th>
<th>Pre</th>
<th>Drugs used perioperatively</th>
<th>Intra</th>
<th>Post</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>15</td>
<td>30</td>
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<td>Skin biopsy and bone marrow biopsy and aspiration</td>
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<td>Sodium thiopental, lidocaine, ketamine</td>
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<td>50</td>
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<td>Bone marrow biopsy and aspiration</td>
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<td>20</td>
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<td>Lidocaine, sevoflurane, nitrous oxide</td>
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Table 3. Preoperative Symptom Frequency and Postoperative Adverse Reactions

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Number of patients (%)</th>
<th>Intraop or postop adverse reaction (%)</th>
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<tbody>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
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<tr>
<td>Flushing</td>
<td>19 (86)*</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17 (77)</td>
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<tr>
<td>Blistering</td>
<td>4 (18)</td>
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<tr>
<td>Gastrointestinal</td>
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</tr>
<tr>
<td>N/V/Diarrhea</td>
<td>10 (45)</td>
<td>4* (18)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (41)</td>
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<tr>
<td>Hepatosplenomegaly</td>
<td>5 (23)</td>
<td>—</td>
</tr>
<tr>
<td>GERD</td>
<td>5 (23)</td>
<td>0</td>
</tr>
<tr>
<td>PUD</td>
<td>2 (9)</td>
<td>0</td>
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<tr>
<td>Neurological</td>
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</tr>
<tr>
<td>Headache</td>
<td>5 (23)</td>
<td>0</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Hypotension</td>
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<td>0</td>
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<tr>
<td>Syncope</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (5)</td>
<td>0</td>
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</tbody>
</table>

Total number of patients = 22.

GERD = Gastroesophageal Reflux Disease; PUD = Peptic Ulcer Disease.

* All 4 patients had nausea and vomiting only.
Tolerability of anaesthesia in patients with mastocytosis in Spain

- 501 patients with mastocytosis (459 adult, 42 children)
- 676 and 50 anaesthesias
- Reported symptoms adults 2% (0.4% anaphylaxis)
  - Reported symptoms children 4% (2% anaphylaxis)
- Risk factors: previous anaphylaxis, major surgeries, general anaesthesia, no premedication ($H_1$, benzos)
- No demonstration of allergy to drugs

=> Preparedness, Emergency awareness, inform anaesthetist, consider premedication (e.g. $H_1$-Antihistamines, benzodiazepins)

Matito et al. Int Arch Allergy Immunol 2015;167:47–56
Mastocytosis passport

Mastozytose-Ausweis

Bitte bei jedem Arzt-, Zahnarzt- und Apothekenbesuch vorlegen. Bei Verlust sofort einen neuen Pass bei Ihrem Arzt anfordern

Deckblatt

Innenseite links

Präventionsmaßnahmen

Nachfolgend aufgeführte Medikamente können als fakultative Histaminliberatoren wirken und sollten vorsichtshalber gemieden werden oder unter ärztlicher Überwachung und ggf. einer Prämédikation mit Antihistaminika und Glukokortikoiden erfolgen.

- Acetylsalicylsaure und andere nichtsteroidale Antiphlogistika
- Morphin, Codein (als Schmerzmittel oder hustenstillende Medikamente)
- Muskelerelaxantien
- i.v.-Anästhetika
- kolloidale Volumenersatzmittel
- Röntgenkontrastmittel

Information: Die aufgeführte Liste enthält keinen Anspruch auf Vollständigkeit und entbindet nicht zur eigenständigen Prüfung der Wirkstoffe.

Mechanische oder thermische Reize können zu einer Mastzelldegranulation führen, daher wird von Sprühungen in heißes oder kaltes Wasser, intensiven Massagen oder Bürstung der Haut auch zu therapeutischen Zwecken abgeraten.

Innenseite recht

Notfallmaßnahmen bei (pseudo-)allergischen Reaktionen

Basismaßnahmen

1.) Fenistil® Tropfen: 1/3 einer N1-Flasche trinken (entspricht 6 von 20 ml)
   Kleinkinder 2 Tropfen/Kg KG
2.) Celestamine® 0,5 N liquidum
   N1-Flasche austrinken (30 ml)
   Kleinkinder 1 InfectoCortiKrupp Supp. rectal

Zusätzlich bei Atemnot/Kreislaufproblemen

3.) Anapen®/Fastjeck®Injektor: Nach Herstellerangaben.

Alternativ bei Atemnot

4.) Kurzwirksames bronchodilatorisches Dosier-aerosol wie Fenoterol (z.B. Berotec®) oder Adrenalin (Primatene® Mist Inhaler) 2-4 Hübe bei Inspiration einatmen, wiederholbar alle 10-15 Minuten.

Notarzt rufen

Rückseite

Klinische Überempfindlichkeitsreaktion auf

☐ anamnestisch bislang nicht aufgetreten.

Folgende Arzneimittel wurden bei Provokationstestung oder im Rahmen einer Dauermedikation anamnestisch vertragen

☐

Stempel des Arztes

Datum Unterschrift des Arztes
KEY POINTS

- Drugs have been implicated as triggers in patients who have mastocytosis associated with anaphylaxis in 18–25% of cases.

- General anaesthesia in patients with mastocytosis is an area of concern and requires specific consideration in the planning of the procedure.

- In unselected patients with drug hypersensitivity, only few patients with unrecognized mast cell disease have been described.

- Nevertheless, in patients with drug anaphylaxis, basal serum tryptase determination and careful skin inspection is recommended to exclude mast cell disease.