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Case Report

Mast Cell Tryptase in a Case of Stevens-Johnson Syndrome – Malpractice, Adverse Event or Disease?

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A B S T R A C T

A 52-year-old male experienced abdominal pain and was referred to hospital. A necrotizing bile-originated pancreatitis was treated by surgery and various intravenous antibacterial medications with combinations. Vancomycin was initiated. A catheter-related infection by Staphylococcus epidermidis was detected, 4 days later blood culture showed Candida albicans and fluconazole was added to medication. Oxycodone was used as pain killer for 4 days at the entry to the hospital. 12 days later cipro floxacillin was added to the treatment. Ten days later all antibiotics were stopped when urticarial rash developed. Cetirizine at 10 mg/day with 240 mg/day iv-hydrocortisone were initiated. Two days later hydrocortisone dose was doubled to 480 mg/day. Oxycodone was readministrated. Also, metabolic acidosis was noted and necrotic parts of pancreas were removed by surgery.

Clinically, the situation worsened rapidly within 2-3 days; exanthema, haemorrhagic purpura with lip lesions and erythrodermia. Clinically, Stevens-Johnson Syndrome was diagnosed. Also, angioedema was detected at face, eye lids and genital area. Patient went to shock and passed away, after 5 days when the skin symptoms started.

As summary, the patient's treatments by antimicrobial medications were justified, but the final diagnosis whether Stevens-Johnson Syndrome was triggered by the medication(s) used or by the infection or both, remains unanswered for sure in this case. Simultaneous atopic response cannot be excluded being able to explain urticarial and partially erythrodermic features.

Keywords: Vancomycin; Exanthema; Stevens-Johnson Syndrome; Metabolic acidosis

Abbreviation: Tryptase; Vancomycin; Fluconazole; Exanthema; Urticaria; Stevens-Johnson Syndrome; Candida albicans; Metabolic acidosis; Pancreatitis

Introduction

The clinical picture of Stevens-Johnson Syndrome (SJS) is somewhat variable and overlaps with Lyell Syndrome with and without blistering. SJS in a serious skin reaction triggered likely by drugs or infection (bacteria, virus, fungi) and may need the treatment at the hospital's Intensive Care Unit. Treatments are individually conducted often by parenteral and topical steroids and antihistamines with pain killers.

Immediate Type I allergic reaction can occur by IgE-mediated or non-specific mechanism, releasing histamine from blood basophils and tissue mast cells. Mast cell release also enzymes (mainly tryptase, chymase, carboxypeptidase A3 and cathepsin G)[1,2], of which the assay of tryptase is used for clinical evaluation for decades.

Histamine has several physiological and pathophysiological roles. The half-life of histamine in blood circulation is very short, about 1-2 minutes due to dilution in the blood volume, but also by two simultaneous enzymatic mechanisms: by Diamine oxidase (DAO) and histamine-N-methyl transferase (HMT) with methyl donor from S-adenosyl-L-methionine already present in plasma at about 26-48 nmol/L concentration[3]. In humans, HMT is the major route. HMT is present in many tissues, but also in blood erythrocytes. DAO is also present in many tissues, in intestine and also in human plasma. If either of these enzymes are inhibited, the elimination of histamine shifts to the alterative pathway[3].

Case Presentation

A 52-year-old non-atopic male experienced abdominal pain and was referred to hospital. A necrotizing bile-originated pancreatitis was treated by surgery and various intravenous antibacterial medications with combinations. Vancomycin was initiated. At the back some infectious eczema areas were noted. A catheter-related infection by Staphylococcus epidermidis was detected, 4 days later the blood culture showed Candida albicans and fluconazole was added to medication. Oxycodone was used as pain killer for 4 days at the entry to the hospital. 12 days later ciprofloxacillin was added to the treatment. Ten days later all antibiotics were stopped when urticarial rash developed. Cetirizin at 10 mg/day with 240 mg/day iv-hydrocortisone were initiated. Two days later hydocortisone dose was doubled to 480 mg/day. Temporarily a short-time tachycardia episode was noted with normal blood pressure. Oxycodone was added. Metabolic acidosis was noted and necrotic parts of pancreas were removed by surgery. During the surgery, patient got alfentanil (Rapifen), fentanyl (Abstral) and rocuronium (Esmeron).

Clinically, the situation worsened rapidly within 2-3 days; exanthema, hemorrhagic purpura with lip lesions and erythroderma. Clinically, SJS was diagnozed. Also, angioedema was detected at face, eye lids and genital area. Patient went to shock and passed away, after 5 days when the skin symptoms started.

Laboratory assays showed serum tryptase level at 285 µg/L (ref. <13,5 µg//L). Blood oxycodone was 0,49 mg/L (therapeutic level 0.01-0,2 mg/L).

Key Questions Related to Literature

- Was it medical malpractice due to excess oxycodone dosing being a histamine liberator causing allergic reaction?
- Was it an adverse reaction to the medication(s) used?
- Was it an infection-triggered Stevens-Johnson Syndrome?
- Was it a newly-developed atopic response simultaneously
- Were there multiple skin diseases simultaneously?

Answers and Discussion

The serum tryptase level was highly elevated. Upon activation of skin mast cells in the type I allergic reaction, histamine and tryptase are released. Histamine can be released also from basophilic blood leucocytes. The body controls effectively histamine effects. The half-life of histamine in blood circulation is very short, about 1-2 minutes due to dilution in the blood volume, but also by two simultaneous enzymatic mechanisms: by DAO in plasma and erythrocyte's HMT with methyl donor from S-adenosyl-L-methionine already present in plasma[3].

Even though plasma histamine radio-enzymatic assay or HPLC with post-column derivatization assay are very sensitive, those are not practical for clinical detection and radio-immuno assay is sensitive for interfering sample constituents without sample's prehandling[3,4].

Urine methylhistamine assay by a 24-hour sample collection may have some value but the base level should be known for comparison. In addition, this analysis needs liquid chromatography-tandem-mass spectrometry or ELISA, the former is not practical for clinical use and the latter should be verified for sensitivity and specificity[3].

Tryptase is highly specific for mast cells[1,2,5-7]. Thus, the commercial serum tryptase assay developed in 1986 by Dr. Lawrence B. Schwartz[8] is more reliable for diagnostics of mast cell activation for at least up to 24 hours after an allergic reaction. However, this assay does not reflect the activation of basophils releasing practically histamine only, since the amount of tryptase from basophils is <1% as compared to release of tryptase from mast cells. In lung- and skin-derived mast cells, mean tryptase levels of 11 and 35 pg per mast cell account for a substantial portion of the cell protein. In contrast, mean levels in peripheral blood basophils (0.05 and 0.04 pg per basophil) are typically less than 1% of those in mast cells, even though histamine levels per cell are similar[9].

Oxycodone is classified as a histamine liberator from mast cells. However, its incidence is not known. Based on our over 30 years of clinical experience, oxycodone is very likely a weak histamine liberator and was not likely the cause of urticaria in this patient, even with the therapeutic level was exceeded by about 3-fold, since the first oxycodone administration some weeks earlier did not cause any signs of clinical histamine release. In addition, during the 2nd oxycodone administration, antihistaminic medication by cetirizine by 10 mg/day and 240 mg/d hydrocortisone were initiated 2 days earlier very likely preventing symptoms of possibly released histamine. Cetirizine at 10 mg/day is a standard official dosing, but it has been acknowledged that it could be added up to 40 mg/day, with clinical experience of safety dosing.

When the patient developed full skin necrosis due to SJS, it is very likely that also skin mast cells became necrotic and released histamine and tryptase. Thus, the interpretation is that highly elevated serum tryptase was mainly from necrotic skin mast cells, not due to allergic reaction by oxycodone. However, it remains unanswered whether cetirizine by 4-fold presently-

accepted "overdosing" would have had a more additional positive effect.

It also should be mentioned that infections can cause urticarial symptoms as histamine liberation via complement activation as well as a cause for exanthematous and purpuric skin rashes and these were clinically detected. Any viral infection, however, simultaneously in this patient was clinically not detected.

While the surgeries went without problems, alfentanil, fentanyl and rocuronium with a rather short half live (90-111 min, 3-7 hrs and 66-80 min, respectively) had no marked influence for the outcome. Of these, rocuronium likely possess the capacity to act as nonspecific histamine liberator and at the same time interfering histamine elimination by inhibiting the HMT-route, as do other muscle relaxants[10].

Leitner et al. have presented that chloroquine and clavulanic acid inhibited highly DAO (> 90%). Cimetidine and verapamil inhibited DAO by about 50%. Moderate influence on DAO was found by isoniazid, metamizole, acetyl cysteine and amitriptyline (>20%). Diclofenac, metoclopramide, suxamethonium and thiamine had a very low inhibition potential (<20%). Interestingly, cyclophosphamide and ibuprofen did not have any effect on DAO[11].

The patient had pancreatitis, thus antibiotic treatment by vancomycin was justified. Simultaneous blood candidosis also justified the treatment by fluconazole. Both of these were used for about 4 weeks and either of them could have triggered the SJS. Patient's earlier medical history did not reveal the use of either medication, but naturally, data obtainable may not be complete.

Because of the severe outcome in case of SJS and Lyell Syndrome, exposition of suspected drugs for the patient would cause ethical issues and fatal outcome, thus, the possible role of both vancomycin and fluconazole as the cause of SJS could have been assayed afterwards several weeks later by a lymphocyte stimulation test from patient's own blood lymphocytes as for confirming the diagnosis in other cases[12,13].

SJS can be triggered by infection and the patient had Staphylococcus epidermidis cultured from catheter site and Candida albicans from blood culture. These may, however, be less likely to cause SJS as compared to the antimicrobial drugs used. Also, the patient had necrotizing pancreatitis.

Theoretically, an atopic response especially for Candida developed within weeks is possible, though would be a rare situation, as described by the fast development of IgE-mediated Type 1 allergy for penicillin[14].

Also, atopic response can develop in older persons than children or younger adults. A 65-year-old male developed erythrodermic atopic dermatitis for his own dog after lived for 15 years together, followed by development of egg white (but not egg yolk) and milk allergies[15]. An 83-year-old female developed atopic dermatitis for home dust mites and storage mites[15]. Thus, the "natural self-made hypo sensibilization treatment" did not work in these two cases.

As connected the above-described development of atopic responses, a human can have multiple skin disorders simultaneously[16] combined with mixing factors, lack of relevant information and unpredicted cross-reactions[14], making the diagnostic measures and treatments a challenge like in a highly-talented but humble detective work being the cheer-up salt for a doctor.

As summary, the patient's treatments by antimicrobial medications were justified, but the final diagnosis whether Stevens-Johnson Syndrome was triggered by the medication(s) used or by the infection or both, remains unanswered for sure in this case. Simultaneous atopic response cannot be excluded being able to explain urticarial and partially erythrodermic features.

Conflict of Interest

Author declares none.

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