

CASE REPORT

PERIOPERATIVE CARE

Perioperative management of a patient with multiple drug hypersensitivity syndrome

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Abstract

Patients with multiple drug hypersensitivity often pose significant challenge during surgery because of the greater risk of developing anaphylactic shock that could be fatal. The use of novel pharmaceutical agents such as anesthetic drugs and medical devices made from a wide range of chemicals and materials with unknown antigenicity potentially predisposes this subset of patients to hypersensitivity reactions in the perioperative period.

The authors encountered a 20-year-old patient with a history of multiple drug hypersensitivities, who had been diagnosed with a huge ovarian tumor. She underwent surgery successfully but faced a rather difficult recovery. Herein, we discuss the management of unexpected perioperative outcomes with the support of literature review. This article also highlights the use of drug provocation tests and the necessary precautions to be taken in the absence of standardized preoperative guidelines for patients with multiple drug hypersensitivity syndrome undergoing major surgical procedures.

Key words: Multiple hypersensitivity; Perioperative; Anesthesia; Suture; Drug provocation test

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1. Introduction

Surgery and anesthesia not only induce stress response, but also expose a patient to different classes of drugs, such as anxiolytics, sedative agents, analgesics, muscle relaxants, antibiotics and antiemetics. Occasionally, vasoactive medications, antihypertensives, antiarrhythmics, hemostatic agents and other emergency medications are also required to stabilize and prevent catastrophic events.

Advancement in pharmaceutical technology has allowed us to produce newer anesthetic drugs with superior pharmacokinetic and pharmacodynamic profiles. However, with better efficacy and efficiency, the underlying antigenicity of most of these drugs remains unclear.¹ As a result, susceptible patients may be exposed to the risk of severe hypersensitivity reactions or anaphylactic shock.²

The authors encountered a patient with underlying multiple drug hypersensitivity syndrome (MDHS),

who underwent major surgery for tumor resection and subsequently faced multiple peri-operative morbidities. We would like to share our experience of its management and emphasize the necessary measures to be taken to deal with such a condition.^{3,4}

2. Case presentation

A 20-year-old nulliparous lady presented with a huge pelvic mass, which had progressively increased in size over 2 months to the size of a 28 weeks gravid uterus. There was no history of weight or appetite loss; however, she had a strong family history of malignancy. She had intermittent asthmatic episodes plus atopic eczema since childhood. She also had multiple episodes of urticaria and skin rashes after exposure to seafood, animal dander, penicillin and cephalixin.

According to her medical records and drug allergy card, medications such as chlorpheniramine, diphenhydramine, bromhexine, cetirizine, paracetamol, mefenamic acid and sulfamethoxazole had been safely prescribed. At the age of 7, she underwent tonsillectomy under general anesthesia uneventfully.

A contrast enhanced CT scan of the abdomen and pelvis was ordered. The patient was prescribed prednisolone 50 mg at 17 hours, 11 hours and 1 hour prior to the imaging according to radiology protocol. Unfortunately, she developed transient urticaria 30 min after taking prednisolone for the initial two doses. Hence, the last dose of prednisolone was replaced with intravenous (IV) hydrocortisone 100 mg. Two minutes after the administration of IV contrast medium, she experienced a generalized flushing, giddiness and difficulty in breathing, which was attributed to a moderate anaphylaxis to contrast medium. Apart from being tachypneic at 30 breath/min, other vital signs were stable and lungs were clear. There was no feature of severe anaphylaxis such as desaturation, hypotension or confusion.^{5,6} She was admitted for observation and subsequently discharged home after a day of observation. Serum tryptase was not performed because she did not fulfill the criteria for severe anaphylaxis which was required for the test in our center.

The patient was referred to an allergy unit and a drug provocation test (DPT) was performed. The report revealed that she developed a hypersensitive reaction to morphine, ciprofloxacin and

ampicillin/sulbactam, for which she experienced shortness of breath and urticaria. She was able to tolerate celecoxib during the DPT.

In view of the huge and well circumscribed tumor shown on CT scan coupled with a significant family history of malignancy, a multidisciplinary decision was made for early surgery as additional testing would have delayed the treatment. Therefore, surgery was planned with strict precautions for any potential anaphylactic reactions.

One day prior to surgery, the patient had another urticarial rash 3 hours after being given polyethylene glycol for bowel preparation. The rash resolved with IV chlorpheniramine and hydrocortisone.

On the day of surgery, inj. chlorpheniramine, hydrocortisone, and fentanyl 2 mcg/kg were administered IV, followed by gas induction with sevoflurane and nitrous oxide. She was paralyzed with cis-atracurium, and doses of fentanyl were topped up every hour in addition to inj. paracetamol 15 mg/kg IV. Prophylactic erythromycin was also given.

The laparotomy was performed with a midline incision. The operative findings revealed a right ovarian tumor measuring 20 cm x 18 cm x 13 cm. Right salphingo-oophorectomy, omentectomy, appendectomy and left para ovarian cystectomy were performed uneventfully, and bleeding was minimal. The abdomen was closed in layers with 3-0 Monosyn® (B. Braun, Germany) sutures, and a subcuticular triclosan coated Stratafix 3-0 suture (Ethicon, Johnson & Johnson, NJ, US) was used to close the skin. Reversal agents were not required as she regained spontaneous breathing with adequate tidal volume prior to completion of surgery.

Postoperatively, patient-controlled analgesia (PCA) with fentanyl, oral paracetamol and celecoxib were prescribed for pain control. Oral erythromycin 400 mg 12 hourly was continued. She was nursed in high dependency unit for close observation.

Two days after the surgery, the patient developed itching, redness and serous discharge around the wound. No systemic symptoms of hypersensitivity were noted. An initial suspicion of hypersensitivity to triclosan suture was made. Further investigation on triclosan was not performed, lest this may induce further hypersensitive reaction and anaphylaxis. She continued to be nursed in the high dependency unit.

The following day, she developed fever with central wound gapping. *Escherichia coli*, resistant to

Table 1: Hypersensitivity history of patient

	Documented Hypersensitivity	No symptom of Hypersensitivity recorded
Documented previously	Penicillin, Cephalexin Seafood Animal dander	Chlorpheniramine, Diphenhydramine, Cetirizine, Paracetamol, Mefenamic acid, Bromhexine, Sulfamethoxazole
Current encountered perioperatively	Prednisolone, Contrast medium, Morphine, Ciprofloxacin, Ampicillin/sulbactam Polyethylene glycols, Bromhexine, Sulfamethoxazole.	Hydrocortisone, Fentanyl, Sevoflurane, Nitrous oxide, Cis-atracurium, Paracetamol, Erythromycin, Gentamycin, Celecoxib, Chlorpheniramine, Cetirizine

erythromycin, was isolated from the wound. The diagnosis was revised to surgical site infection due to non-optimized antibiotic use. Erythromycin was discontinued and tablet sulfamethoxazole was started. However, the patient developed urticaria and itching 30 min after taking sulfamethoxazole. Subsequently, she was put on IV gentamicin and daily wound dressing with normal saline was done.

Five days after surgery, the patient developed cough, for which oral bromhexine was prescribed. She developed multiple episodes of urticaria within an hour each time after taking the medication. She was instructed to perform breathing exercise using incentive spirometry while bromhexine was taken off her prescription. In view of her postoperative morbidity and frequent hypersensitive responses, the patient was discharged after completing the full course of antibiotics. Secondary suturing was successfully performed one month later with Dafilon suture. Histopathological report of the removed mass revealed a borderline type International Federation of Gynecology and Obstetrics (FIGO) stage 1A1 ovarian tumor. She subsequently recovered, with life-long surveillance and regular follow up with the gynecologist.

3. Discussion

Multiple drug hypersensitivity syndrome (MDHS) refers to a subset of patients who are prone to develop hypersensitive reactions against a variety of structurally unrelated drugs. Typical clinical

presentations of acute urticaria, angioedema or both are due to abnormal cross-reactivity between different medications and/ or food.⁷ Despite this condition being increasingly recognized, the exact mechanism of MDHS is still not fully understood.⁸

This case report demonstrates the perioperative challenges in managing a patient with MDHS undergoing major surgery. Current literature and guidelines concerning the perioperative management of MDHS is still lacking.^{7,9,10} Insufficient hypersensitivity testing also cause these patients to be inappropriately managed.

Therefore, apart from keeping a good clinical history, specifically on exposure to allergens, food, medication and anesthesia history, it may be beneficial for MDHS patients to undergo skin testing or DPT for all the medications that are planned to be used perioperatively.^{11,12}

Interestingly, patients with MDHS can still develop hypersensitivity reactions towards a similar drug that was initially reported to be negative. The drug allergy card of this patient clearly stated that she is not hypersensitive to sulfamethoxazole and bromhexine. However, she still developed hypersensitive reactions to both these drugs (Table 1).

Drug hypersensitivity appears in various patterns, i.e. immediate¹³ or delayed hypersensitivity reactions.¹⁴ The first exposure to an allergen or medication may cause sensitization without any significant symptoms.¹⁵ Nevertheless, one has to be

cautious as this does not rule out severe reactions in subsequent exposures. Besides, mild hypersensitive reactions have been reported to precede severe anaphylactic reaction.¹⁶ Thus, the practice of simplifying and minimizing perioperative medications is highly recommended.

In our patient, the type of hypersensitivity reactions which occurred are mostly immediate in nature. These can either be allergic responses (immune mediated) or non-allergic responses (non-immune mediated / pseudo allergic / anaphylactoid reactions).¹⁷ Non-allergic hypersensitivity is usually a consequence of direct, pharmacological or substance stimulation of mast cells and basophils, leading to the release of inflammatory mediators. It does not involve immunological mechanism and hence previous exposure to the substance is not required.¹⁸ However, clinical manifestation and management in non-allergic anaphylaxis remains the same.

MDHS is also associated with anxiety and depression,¹⁹ thus in the stressful perioperative period of major surgery followed by a potentially longer hospital stay, the psychological aspect of the patient needs to be carefully addressed.

Mode of Anesthesia

As for anesthesia, the best modality for MDHS patients going for major surgery remains general anesthesia with endotracheal intubation. This will secure the airway, in the event of anaphylaxis that may manifest during surgery. Regional anesthesia and nerve blocks may offer benefits when it is compatible with the surgery, if the patient is not hypersensitive to local anesthetic drugs. The worst scenario anticipated is that of anaphylactic shock with cardiovascular complications. Thus, close monitoring with emergency medications (i.e. epinephrine) on standby is of utmost essential.

Antibiotic Selection

The wound dehiscence in this patient was initially thought to be due to hypersensitivity to triclosan coated sutures, until a wound swab cultured E-Coli. Patients with antibiotic hypersensitivity tend to be managed with unoptimized antibiotics.⁹ Literature has shown that among patients with penicillin allergy, there is a 50% higher risk of surgical site infections, due to compromised administration of second-line perioperative antibiotics.²⁰ This issue should be anticipated and addressed carefully before a major surgery of a patient with MDHS.

Suture Material and Surgical Site Infection

The choice of suture used in abdominal surgery is of paramount importance because inappropriate selection of suture material may result in hypersensitive reactions, wound dehiscence and delayed healing.^{21,22}

Stratafix suture is coated with triclosan which is an antibacterial and antifungal agent. Although it has been proven to reduce surgical site infection,²³ triclosan allergy have been reported.²⁴⁻²⁷ Unfortunately, we were unable to perform a hypersensitivity test to triclosan in this patient.

Sutures are foreign bodies that may cause local immune responses, which compromises the ability of the body to fight local infections.²⁸ The preferred suture material in patients with MDHS should be non-coated synthetic sutures which have low antigenicity and less inflammatory infiltrates.^{29,30}

Guidelines

Perioperative protocols though available, only focus on perioperative anaphylaxis.^{10,31} A complete perioperative management guidelines focusing on all different aspects for patients with MDHS is still needed.

The authors emphasized that special consideration and precautionary measures should be taken for patients with MDHS despite preoperative tests. These encompasses preoperative preparations including skin testing, DPT and the use of minimum medications, from bowel preparation, skin cleansing agents, antibiotics, latex free apparatus, to caution in selection of sutures and dressing materials, as well as the psychological wellbeing of the patient.

Role of Drug Desensitization

For the past decade, drug desensitization has been suggested as a treatment for drug hypersensitivity.³²⁻³⁴ This practice can involve IgE or non-IgE immune mechanisms. All protocols of drug tolerance induction involve gradual subtherapeutic dose increment of the specific drug.

Drug desensitization is particularly important when there is no drug alternative or when the particular medication is critically needed. It has been shown to be useful in anticonvulsants, antituberculosis,³⁵ chemotherapy, antimicrobials,³⁶ NSAIDs,³⁷ and immunotherapy.³⁴

The role of drug desensitization has been described in perioperative patients,^{38,39} however, its

implementation is not widely done, probably due to the availability of a wide variety of alternative medications. With the development of safe desensitization practices, first-line medication desensitization may be the preferred option even when the alternative is available. It may be particularly useful for patients with MDHS.

4. Conclusion

A thorough and systematic perioperative evaluation of patients with MDHS is mandatory in order to minimize postoperative morbidity and mortality. Judicious use of simple medications should be emphasized in order to avoid unexpected hypersensitive reactions.

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6. Conflict of interest

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7. Author contributions

All authors had access to the data and were involved in writing the manuscript. ZAG and SEC drafted the manuscript; SS, VML, JAL and SEC performed literature search, revised the content and completed the manuscript. All authors involved directly in the discussion, performed proofreading and approved the final manuscript.

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