Chemotherapy Related Angioedema

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Dear Editor,

We read the case report titled “Intraoperative Ephedrine Allergy in a Patient Who Received Chemotherapy and Perioperative Hypersensitivity Reactions” by Hakimoğlu et al. (1) with great interest. The authors reported that diffuse urticarial hypersensitivity reaction, which was associated with the administration of intraoperative ephedrine, was observed in a patient with no history of a known allergy to any drug, having received chemotherapy (CT) because of breast cancer (ca) and having used a single dose of 20 mg tamoxifen a day. In this study, ephedrine allergy, which is a rarely observed situation, was successfully explained, but its relationship with CT was not adequately mentioned as stated in the title of the study.

Angioedema can be generally examined under two main headlines, i.e. as mast cell- and bradykinin-related angioedema. Mast cell-related angioedema develops because of allergic reactions, and these patients have accompanying urticaria. These patients benefit from anti-histaminic therapy because of the presence of an allergic reaction. In contrast, bradykinin-related angioedema occurs when bradykinin causes increased vascular permeability. Moreover, urticaria is often not observed in these patients, and no response to anti-histaminic agents is obtained (2, 3).

Although drug-related angioedema after chemotherapy is an uncommon condition, it has clinical importance because it can lead to serious results (4). In the pre-operative evaluation of a patient by anaesthesiologists, CT application, CT duration, last CT application date and drug allergy are particularly investigated. If a patient presents an allergy, its additional effects should also be questioned. In our clinic, angioedema was encountered in the upper respiratory tracts of two patients who were administered CT for breast cancer (ca). One of the patients was intubated, but tracheostomy was required for the other because intubation could not be performed.

Our first case was a 47-year-old female patient who had undergone mastectomy because of breast ca 1 year ago and whose CT was ongoing. She visited the emergency unit with respiratory distress because of angioedema, and a tracheostomy was urgently opened because she could not be intubated. She was then followed up in the intensive care unit for 2 days with the tracheostomy maintained. Then, her angioedema findings regressed, and she was transferred to the clinic after closing tracheostomy on the third day.

Our second case was a 55-year-old female patient who visited for lumbar disc herniation (LDH). It was learned from her history that she had been operated once under general anaesthesia (1.5 years ago, mastectomy) and once under spinal anaesthesia (6 months ago, hysterectomy), and she had not had any problems because of mastectomy performed under general anaesthesia. Chemotherapy had been applied after mastectomy, and a single dose of 2.5 mg letrozole therapy (Femara, Novartis) had been initiated for maintenance. It was learned that after therapy, she had visited the emergency unit four times because of angioedema, and she had been intubated once for this reason.

In the second surgery of the patient that was performed for endometrium ca, spinal anaesthesia was administered to avoid polypharmacy because of the history of frequent angioedema. No problem was encountered during the intervention. After she was taken to the recovery room, she reported nausea, and therefore, she was intravenously administered 4 mg ondansetron. After approximately 5 min, she stated that she could not breathe and her lips swelled, and she developed respiratory arrest. She was intubated with difficulty through a balloon-valve mask and intubated with rapid sequence induction. Then, she was taken to the intensive care unit for close monitorization. After 24 h, the requirement for intensive care dissipated, and she was transferred to the clinic.

In the third surgery of the same patient for LDH, she was tested for any allergy to drugs that were used in the routine anaesthesia practice, in accordance with the recommendation of the consulting physician from the Department of Internal Di-

seases. The results of the allergy tests were positive to vecuronium, atracurium and mivacurium from the muscle relaxants, H2 receptor blockers and NSAIs and ondansetron as anti-emetic. Therefore, the patient, who refused regional anaesthesia application, was not administered these drugs before, during or after the operation.

After possible risks were explained to the patient, she was taken to the operating room, and no complications developed during the perioperative period. Then, she was extubated and kept under control in the recovery room for approximately 2 h. With the recommendation of monitorization, she was transferred to the clinic.

The patient's history of no complication in the first surgery that was performed under general anaesthesia, hypersensitivity symptoms increasing after CT and ondansetron-induced angioedema that developed after spinal anaesthesia led us to be more careful in the last operation. In patients receiving CT, changes in the immune system activate a classical complement system, such as hereditary angioedema physiopathology, and can cause a decrease in C1q and an increase in the bradykinin level without any change in the C3 level (3, 4). Clinical reflection of this condition is intermittent angioedema of subcutaneous tissues without itching, and bradykinin is demonstrated as the responsible agent (5). It has been reported that this condition is generally observed in patients with C1INH deficiency (3). Because in the laboratory of our hospital, the C1INH level could not be examined, its level in our patient was not controlled. In patients with a low level of C1INH, concentrated C1INH (ceter), concentrated kallikrein inhibitor (ecalantide), B2 bradykinin receptor antagonists (Icatibant), fresh frozen plasma and corticosteroids are used for treatment (5).

Similar to the case of Hakimoğlu et al. (1), our patients had no history of a known allergy to any drug before chemotherapy. Because it is known that many drugs used in anaesthesia practice at present can cause anaphylactoid and anaphylactic reactions, the basis of the anaesthetic approach for patients receiving CT should include avoiding factors that could lead to this situation, taking necessary precautions and avoiding polypharmacy.

References

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Author's Reply

Dear Editor,

We thank the honourable author for his/her commentary and contributions regarding our article titled "Intraoperative Ep-

hedrine Allergy in a Patient Who Received Chemotherapy and Perioperative Hypersensitivity Reactions", which was published in the Turkish Journal of the Anaesthesiology and Reanimation.

It was mentioned in our article that the responses to allergens after chemotherapy (CT) could differ. However, there are few cases and studies published in the literature regarding this issue. Therefore, we could not demonstrate a case as a reference in the discussion section. Furthermore, our aim was to report an allergic reaction that developed after ephedrine administration and changed the allergic response by CT and to explain the approaches of diagnosis and treatment in patients having an allergic reaction.

The author presented two angioedema cases reporting that changes in the immune system after CT were similar to the clinical picture of inherited angioedema. However, there are no non-clinical data demonstrating a quantitative or functional defect of the first component inhibitor of the complement. Factors causing angioedema also include histamine, PGD₂, platelet activating factor (PAF), leukotrienes (C and D), anaphylatoxins (C3a, C4a and C5a), histamine releasing factor and chemokines, as well as bradykinin.

Therefore, it is difficult to say that the clinical picture developing after CT is associated with complement deficiency. In our case, skin reaction occurred after the administration of ephedrine. We mentioned that the increased IgE level suggested drug allergy from type 1 (IgE-mediated) allergic reactions and the specific IgE was not evaluated. In this reaction, mast cells are activated through IgE antibodies. The clinical picture then develops with the effect of the released mediators (histamine, tryptase, leukotrienes, etc.) on the veins.

The two cases shared by the author are consistent with our thoughts that CT changes the responses of patients to allergens. We suggest that further clinical studies supported with laboratory findings are needed to reveal through which mechanism CT changes the responses to allergens.

Yours sincerely,

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