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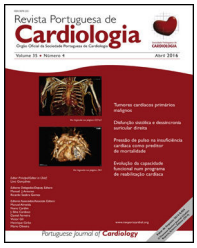

LETTER TO THE EDITOR

Quinolone-induced hypersensitivity reactions and the Kounis syndrome

Reações de hipersensibilidade induzidas por quinolona e a síndrome de Kounis

In the very interesting paper by João Almeida et al. published in the *Journal*,[1] an 85-year-old hypertensive man, a former smoker, allergic to quinolones, with bladder cancer and chronic kidney disease and taking hydroxyzine and alprazolam, developed a type I variant Kounis syndrome in the operating theater immediately after administration of ciprofloxacin. Following suspension of ciprofloxacin and treatment with morphine, aspirin and ticagrelor the patient recovered. Coronary arteriography was normal, troponin was slightly elevated and the patient had leukocytosis with neutrophilia.

This report raises important questions concerning the role of the drugs the patient had taken before the operation, quinolone treatment, the presence of neutrophilia and morphine administration.

1. The described patient was allergic to quinolones and was taking the antihistaminic agent hydroxyzine and the benzodiazepine-class anxiolytic alprazolam, followed by administration of ciprofloxacin in the operating theater. He developed constricting chest discomfort associated with dyspnea, sweating and hypotension. Hydroxyzine and alprazolam can rarely and unexpectedly induce allergic reactions such as cutaneous drug eruption[2] and cold-induced urticaria,[3] respectively. It seems likely that these three agents could have acted as a dangerous antigenic triplet able to induce allergic mediator release and Kounis syndrome. Indeed, clinical studies have shown that atopic patients allergic to and simultaneously exposed to several antigens have more symptoms than monosensitized individuals.[4] At the same time, IgE antibodies with different specificities can have an additive effect, and even sub-threshold numbers of these antibodies can join forces and trigger allergic mediator release when the patient is simultaneously exposed to the corresponding antigens.[5]
2. Fluoroquinolones are generally considered well-tolerated antibiotics, but their consumption is steadily increasing. Kounis syndrome has been induced not only by ciprofloxacin, but also by levofloxacin[6] and the original quinolone cinoxacin.[7] Indeed, ciprofloxacin-induced Kounis syndrome, apart from the case currently under discussion, has been reported in one additional case.[8]

   It is anticipated that more cases will appear in the future. Therefore, a high index of suspicion seems to be important.
3. Morphine and other opiates and opioids can induce anaphylactic reactions via mast cell degranulation that continue to cause concern. IgE antibodies to morphine and codeine have been detected in the serum of at least one subject who experienced a life-threatening anaphylactic reaction following the administration of a combination of papaveretum and hyoscine.[9] Indeed, Kounis syndrome has been also induced by morphine administration in two patients.[10,11]

   The described patient was fortunate when he received treatment with morphine, aspirin and ticagrelor for his constricting chest discomfort associated with dyspnea, sweating and hypotension and had an uneventful recovery. Fentanyl and its derivatives show little mast cell activation and are preferable.
4. The described patient had coronary angiography, performed two hours after symptom onset, that excluded coronary disease. However, he had slightly raised high-sensitivity troponin levels with leukocytosis and neutrophilia during the anaphylactic event that denote type I variant Kounis syndrome attributed to coronary spasm. Indeed, leukocytes and polymorphonuclear neutrophils as well as other inflammatory markers have been found to be significantly associated with coronary artery spasm.[12]
5. We entirely agree with the authors of this report[1] that there is no consensus on treatment for Kounis syndrome, and most of the data on it are from case reports. However, a large group of eminent cardiologists, immunologists, allergists, anesthetists and surgeons have agreed to convene in order to establish diagnostic and treatment criteria, and we urge any scientist with interest and experience in this syndrome to participate.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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