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Case Report

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Agranulocytosis Associated with Trandolapril-Verapamil Combination

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Abstract

A number of medications have been implicated as potential causes of severe neutropenia or agranulocytosis. A 66-year-old female patient was administered with verapamil-trandolapril for treatment of hypertension. Over three years of verapamil-trandolapril treatment, neutropenia developed. Verapamil-trandolapril was switched to amlodipine and white blood cell count recovered within two months. After a while, amlodipine was switched to ramipril because of the pretibial edema (a side effect of amlodipine); over thirty days neutropenia developed once again. Agranulocytosis is rarely seen due to angiotensin converting enzyme (ACE) inhibitors. Therefore, physicians should be aware of the potential side effects of ACE inhibitors and their combinations on blood cells (especially neutrophils), particularly in patients treated for a long time.

Keywords: ACE inhibitor; Agranulocytosis; Drug induced neutropenia; Neutropenia; Ramipril; Trandolapril; Verapamil

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Introduction and General Information

Neutropenia is defined as a decline in the neutrophil count to a level below 500/µl, which generally occurs after chemotherapy or radiotherapy [1], and as it is predicted to develop, it is treated with G-CSF therapy[2-4]. Neutropenia may also be induced by analgesic/anti-inflammatory drugs[5-8] angiotensin converting enzyme (ACE) inhibitors[9-12], antipsychotics, oral antidiabetics and antithyroid drugs. Several clinical cases of agranulocytosis, neutropenia or neutropenic fever, induced by various drugs, have been reported in the literature in the form of case reports or case series. In this case report, we present a case developing agranulocytosis induced by trandolapril-verapamil combination, as well as the relevant therapeutic approach, aiming to draw attention to a rare side effect of this commonly used drug and raise awareness.

Case Report

A 66-year-old woman with diabetes mellitus and hypertension presented to our internal medicine outpatient clinic with the complaints of fever and dysphagia. The patient's body temperature was measured as 37.9°C and her complete blood cell count (CBCC) revealed the leukocyte count of 880/µL (neutrophil 10/µL), hemoglobin 12.3 g/dl, hematocrit 36.5%, and platelet count 292,000/µL. The patient was receiving "verapamil-trandolapril" combination for hypertension for about three years, along with subcutaneous insulin for diabetes mellitus. The evaluation of her peripheral blood smear by a hematology specialist was associated with a "suspicious" blast-like cell, and a bone marrow biopsy was performed. Bone marrow aspiration biopsy specimen showed

a marked increase in myeloid-granulocyte series, an M/E ratio around 2/1, normal erythroid series and cellular proliferation in lymphoid series, normal megakaryocytes both in number and degree of maturation, with no atypical blastic cells. Thus, findings suggested a toxic agent. In addition, it confirmed that the patient had no benign or malignant myelodysplastic or infiltrative disease. Patient's previous CBCC results were revealing that her absolute neutrophil count had gradually declined over the years (September 2011: 2000/µL, January 2012: 1200/µL, November 2012: 800/µL). The serological tests for the etiology of agranulocytosis, as well as autoantibodies test and four blood cultures taken from the patient, resulted in negative, while the results of the measurements for thyroid functions, vitamin B12 and folate levels were also within normal range. The thorax CT scan detected no significant pathology and her echocardiography findings were normal. As trandolapril, the active ingredient in the verapamil-trandolapril combination used by the patient is known to cause agranulocytosis as a side effect and none of the other drugs she had been using had been reported to cause agranulocytosis as a side effect. The drug was discontinued and a therapy with "amlodipine" 10 mg once daily was started. The patient also had a tinea pedis infection, which was successfully treated with a topical anti-fungal therapy. During the hospitalization period, the patient's body temperature never rose above 36.9°C, while her neutrophil levels began to improve gradually after the discontinuation of the drug containing trandolapril, which we considered the cause of neutropenia. About a week later, her neutrophil count increased to a level of 370/µL. She was discharged with a healthy condition. CBCC on the day 20 after the discontinuation of drug showed a leukocyte value of 4300/mm3 and a neutrophil count of 2000/µL. The CBCC at day 50 after the discontinuation of the drug showed that leukocyte level was 4350/mm3 and neutrophil count 2260/µL, and then the patient's follow-up was continued. Three months after the discharge, she once again presented to the emergency department with a complaint of swollen feet. The swelling of the feet was associated with the amlodipine therapy, and thus amlodipine was discontinued. After the initiation of the treatment with ramipril 5mg/day, the patient's neutrophil count declined once again to a level of 1100/µL. Considering that ramipril might also cause agranulocytosis, the patient's antihypertensive treatment was administered as nifedipine 60 mg/day. In the follow-up, CBCC of the patient showed no significant decline in leukocyte and neutrophil values.

Discussion and Conclusion

A neutrophil count below 1500/µL in the CBCC during 1-3 weeks of follow-up after the drug use and the absence of additional pathologies that may cause neutropenia suggest a diagnosis of drug-induced neutropenia. Fever is generally the first symptom of the drug-induced neutropenia[13]. ACE inhibitors, which are used for the treatment of congestive heart failure and hypertension, have been reported to cause neutropenia as a side effect, though rarely. The most commonly reported cases in the literature mainly include neutropenia cases induced by captopril[9-12,14-15], with some cases associated with the use of enalapril[16] and ramipril[17].

There are two basic mechanisms in drug-induced neutropenia and/or agranulocytosis[18-22]:

• Immune-mediated destruction of neutrophils by the circulating antibodies induced or stimulated by drugs

• The direct toxic effect of the drug on the granulocytic precursors in the bone marrow

In our case, a gradual decline occurred in the neutrophil count during the use of trandolapril, an ACE inhibitor, whereas an improvement was observed in the neutrophil count following the discontinuation of the drug. The neutrophil count that recovered after the discontinuation of trandolapril decreased again below the level of 1500/µL after the patient began to use ramipril (another ACE inhibitor) three months later. That suggests that the neutropenia side effect of those drugs could actually be a class effect. The bone marrow aspiration smear, which was performed at the time of diagnosis, showed a significant reduction in the myeloid series. That indicates that the drug metabolites have a toxic effect on myeloid-granulocyte series, the precursors of neutrophil series, and reduce the production. Therefore, the main cause of neutropenia is not the destruction in the periphery, but such reduction in the production of bone marrow is due to the toxic effect of the drug.

The specific risk factors for agranulocytosis might include the following:

• Advanced age (>50 years)[23]

• Female gender (70% of the cases are women)[24-25]

• A history of infectious mononucleosis[26]

• Chronic renal failure in patients using captopril or insufficient urinary excretion of the drug in patients receiving concomitant probenecid[27]

• Therapy with a combination of ACE inhibitors and interferon (particularly high risk)[28]

• The presence of underlying autoimmune disease[29]

As can be seen, our patient's gender (female) and advanced age (66 years) were among the factors that predisposed to development of agranulocytosis.

After the initiation of drugs known to cause neutropenia, CBCC, and peripheral smear examinations should be performed at regular intervals during the first three months for an earlier diagnosis. Still, long-term use of those drugs should be avoided in patients with autoimmune diseases, such as systemic lupus erythematosus and systemic sclerosis, since such patients are at higher risk of developing neutropenia[29].

In the cases of drug-induced neutropenia, the main treatment principle is the discontinuation of the drug. The previous studies reported that the neutrophil count normalized within 3 to 56 days after the drug was discontinued[30-32]. The diagnosis is confirmed by the increasing neutrophil count following the discontinuation of the drug. If a low neutrophil count is accompanied by a clinical infection and fever, blood samples, urine and throat cultures should be immediately obtained and a broad-spectrum antibiotic therapy should be initiated[33]. If there is a marked decrease in the neutrophil count (below 500/µL), an additional therapy with granulocyte-colony stimulating factor (filgrastim or lenograstim 5mcg/kg/day) may be administered subcutaneously or intravenously (for about 5-7 days) until the neutrophil count increases over 1500/µL[34-38].

In our case, such cultures were obtained and there was no growth. With a healthy condition, the patient was discharged at day 7 with scheduled outpatient follow-up visits. Her neutrophil count was measured as 2000/µL at day 20 after the discon-

tinuation of drug.

In conclusion, neutropenia or profound neutropenia (called agranulocytosis if neutrophil count is below 500/μL)[39] may occur within 5-7 days, or even later, following the use of any drug. This case report aims to draw attention to neutropenia that develops through a toxic effect on the myeloid-granulocyte series induced by verapamil-trandolapril, a combination of anti-hypertensive agents commonly used for the treatment of hypertension, which is one of the most common diseases in today's world the discontinuation of the drug and the use of neutrophil-stimulating cytokines, as well as an appropriate antibiotic therapy for infections in the presence of fever provide a near-complete clinical and laboratory recovery within 3-5 days in such cases.

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