Three Cases of Vasospastic Angina that Developed Following the Initiation of Corticosteroid Therapy

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Abstract

Three patients diagnosed as having remitting seronegative symmetrical synovitis with pitting edema syndrome, pemphigus erythematosus and idiopathic interstitial pneumonia were treated with oral prednisolone. Several weeks after starting the treatment, they experienced repeated chest pain attacks between midnight and early morning, although none of the patients had a past history of ischemic heart disease. One of the patients exhibited aggravation of symptoms soon after increasing the dose of prednisolone. A definitive diagnosis of vasospastic angina was made using electrocardiograms, coronary angiography and vasospasm provocation tests. These cases emphasize that clinicians should be aware of the possible occurrence of vasospastic angina following the initiation of corticosteroid therapy.

Key words: vasospastic angina, coronary spasm, corticosteroid, prednisolone


Introduction

Vasospastic angina is caused by myocardial ischemia due to transient abnormal vasoconstriction of the coronary arteries. Anginal attacks with ST segment elevation or depression on electrocardiography often occur between midnight and early morning. It is well known that several physical factors and pharmacological agents precipitate coronary spasms. The former include physical and mental stress, exposure to cold and hyperventilation. The later include various agents such as alcohol, smoking, acetylcholine, serotonin, histamine, ergonovine, catecholamines, beta-blocking agents, etc. However, reports of coronary spasms caused by corticosteroids are relatively rare.

Corticosteroids are widely used to treat autoimmune and allergic diseases. Adverse effects on the progression of atherosclerotic cardiovascular disease are often observed during corticosteroid therapy because corticosteroids can exacerbate coronary risk factors, such as hypertension, hypercholesterolemia and impaired glucose tolerance. On the other hand, an association between corticosteroids and coronary spasms has not yet been documented. In this report, we present three cases of patients who developed vasospastic angina after starting corticosteroid therapy and discuss the possibility that coronary spasms may be induced by corticosteroids.

Case Reports

Case 1

A 79-year-old woman visited her local doctor complaining of bilateral swelling of the hands and arthralgia in the upper limbs. The administration of nonsteroidal anti-inflammatory drugs for several weeks failed to improve her symptoms, and she was diagnosed as having remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome based on her clinical features, such as the sudden onset of symptoms, presence of symmetrical polyarthritis with prominent pitting edema and negative rheumatoid factor results. Treatment with oral prednisolone (PSL) at a dose of 15 mg/day effectively relieved her symptoms. Approximately one month after starting corticosteroid

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therapy, she complained of transient chest pain while walking in the morning. Subsequently, chest pain attacks of short duration often occurred at rest in the early morning hours. A 24-hour Holter recording revealed transient ST segment elevation during a chest pain attack that lasted for two minutes and was relieved by the administration of sublingual nitroglycerin (Fig. 1A).

The patient was therefore referred to our hospital for a further investigation. In her clinical history, she had experienced no chest pain attacks until the start of corticosteroid therapy. She did not smoke or drink alcohol. Routine laboratory tests revealed no significant abnormalities, except for elevation of the low-density lipoprotein (LDL) cholesterol level (191 mg/dL). Coronary angiography showed no significant stenosis, except for 50% stenosis in the middle segment of the right coronary artery (RCA) (Fig. 1B). A coronary spasm provocation test was therefore performed. Following the intracoronary administration of 20 μg of acetylcholine, 99% occlusion appeared in the middle segment of the RCA, which was relieved by an intracoronary infusion of isosorbide dinitrate (Fig. 1C, D). A definitive diagnosis of vasospastic angina was made, and treatment with 100 mg/day of extended-release diltiazem was started. In addition, the hypercholesterolemia was treated with 2.5 mg/day of rosvastatin. The coronary spasms were effectively controlled, and the corticosteroid therapy for RS3PE syndrome was continued with gradual tapering of the dose of prednisolone. During the 1-year follow-up period, there was no relapse of anginal symptoms.

Case 2

A 60-year-old man visited a local dermatologist with a 1-year history of vesiculobullous eruptions on his face, trunk and extremities. Following the initiation of treatment with oral PSL at a dose of 10 mg/day, he often experienced mild chest oppression for a few minutes between midnight and early morning.

Five months after starting steroid therapy, he was admitted to the department of dermatology at our hospital due to aggravated cutaneous lesions. He was a nonsmoker and social drinker. He had a history of hypertension beginning at 53 years of age and had been treated with 5 mg/day of enalapril. Laboratory tests revealed no significant abnormalities, except for elevation of the total cholesterol level (243 mg/dL) and positive anti-desmoglein 1 antibodies. A definitive diagnosis of pemphigus erythematosus was made on a skin biopsy, and the dose of oral PSL was increased to 50 mg/day.
Two days after the steroid dose was increased, the patient experienced repeated transient chest pain attacks three times between midnight and early morning. The attacks lasted approximately one minute and disappeared spontaneously. He subsequently developed more severe chest pain lasting for a few minutes the next day, at which time, a 12-lead electrocardiogram revealed transient ST segment elevation in leads II, III and aVF (Fig. 2). Therefore, he was referred to the cardiology department. A diagnosis of acute coronary syndrome was suspected and continuous intravenous infusions of isosorbide dinitrate and unfractionated heparin were started. While emergent coronary angiography showed mild luminal irregularities in the left coronary artery, neither significant stenosis nor thrombotic lesions were observed. A diagnosis of vasospastic angina was made, and treatment with 200 mg/day of extended-release diltiazem was started. In addition, the hypercholesterolemia was treated with 5 mg/day of pravastatin. These medications were effective in controlling the patient’s chest pain attacks, and the corticosteroid therapy for pemphigus erythematosus was continued with gradual tapering of the dose of PSL. During a follow-up period of 15 months, no relapse of vasospastic angina was observed.

Case 3

A 65-year-old man was referred to our hospital with a 3-month history of a fever, dry cough and appetite loss. He had been treated with antibiotics at his local hospital without improvement. He smoked 10 cigarettes per day and did not drink alcohol. He had no history of diabetes mellitus. A chest X-ray showed ground glass opacity with consolidation in the bilateral lower lung fields. Laboratory tests revealed the following values: WBC count= 7,800/mm$^3$ (81.5% neutrophils, 9.7% lymphocytes); C-reactive protein (CRP)=5.9 mg/dL; lactate dehydrogenase (LDH)= 341 IU/L; KL-6= 1,340 U/mL (<500); and SP-A= 221 ng/mL (<43.8). Antinuclear antibodies, proteinase-3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) and myeloperoxidase (MPO)-ANCA were negative. An analysis of the bronchoalveolar lavage fluid revealed increased lymphocytes. Based on these findings, a diagnosis of idiopathic interstitial pneumonia, particularly cellular nonspecific interstitial pneumonia (NSIP), was suspected, and treatment with prednisolone at a dose of 30 mg/day was started on the second hospital day. The corticosteroid therapy relieved the patient’s symptoms, and the dose of PSL was reduced to 25 mg/day on the 12th hospital day. In the early morning of the 28th hospital day, the patient experienced chest oppression after walking to the toilet in the ward. The symptoms lasted for approximately one hour and spontaneously disappeared. Three days later, he experienced similar transient chest oppression. He was then referred to the cardiology department for detailed examinations. While coronary angiography showed diffuse luminal irregularities in the coronary arteries, neither significant stenosis nor thrombotic occlusion were observed (Fig. 3A). A coronary spasm provocation test with 20 μg of acetylcholine demonstrated 99% occlusion of the right coronary artery, which was promptly relieved by the intracoronary infusion of isosorbide dinitrate (Fig. 3B, C). A definitive diagnosis of vasospastic angina was made, and treatment with
100 mg/day of extended-release diltiazem was started. Pravastatin (5 mg/day) was also given to treat the dyslipidemia (total cholesterol: 297 mg/dL, high-density lipoprotein (HDL) cholesterol: 74 mg/dL, triglycerides: 224 mg/dL). The treatment of interstitial pneumonia with 25 mg/day of PSL was continued for approximately six weeks, after which the dose of PSL was gradually tapered. The patient’s coronary spasms were well controlled, and he exhibited no relapse of angina during the 16-month follow-up period.

**Discussion**

We herein described three cases of vasospastic angina that occurred following the initiation of corticosteroid therapy. In these cases, none of the patients had a past history of ischemic heart disease and initially developed chest pain within at least one month after starting the corticosteroid therapy. They were not given any other drugs that can precipitate coronary vasospasms. In addition, the second patient developed aggravation of vasospastic angina only two days after the dose of PSL was increased from 10 to 50 mg per day. The patients had been suffering from various immunologic diseases, including RS3PE syndrome, pemphigus erythematosus and idiopathic nonspecific interstitial pneumonia; however, vasospastic angina is not a common complication of these diseases. Collectively, these facts appear to corroborate the existence of a close relationship between the administration of corticosteroid therapy and the development of vasospastic angina. Several experimental and clinical reports have demonstrated a link between corticosteroids and vasospasms. Interestingly, Hizume et al. reported that the oral administration of cortisol directly induced hyperconstriction of the coronary arteries, based on cortisol’s function as a stress hormone, on vasospasm provocation tests during coronary angiography in pigs (1). In accordance with this result, it is possible that corticosteroids per se directly induced the development of vasospastic angina in our patients.

A decreased nitric oxide activity caused by endothelial dysfunction and the hypercontractility of coronary smooth
muscle cells due to Rho-kinase activation are together thought to play an important role in the pathogenesis of vasospastic angina (2). In this context, several studies have shown that glucocorticoids inhibit endothelium-dependent vasodilation and sensitize coronary vasoconstriction responses via Rho-kinase activation (1, 3-5). Therefore, we speculate that the vasospastic angina observed in our cases was caused by the adverse effects of corticosteroid therapy on the coronary endothelium or smooth muscle cells. In addition, it has been reported that the occurrence of vasospastic angina is associated with the presence of occult atherosclerosis at the site of the coronary vasospasm, even in the absence of angiographically significant stenosis (6, 7). Indeed, in all our cases, coronary angiography demonstrated mild atherosclerotic changes without significant stenosis. These coronary atherosclerotic lesions may also have been an important factor leading to the development of vasospastic angina in our patients.

Previous case reports have described the occurrence of coronary spasms following corticosteroid administration (8, 9). The cause of the vasospasms in these cases was thought to be an allergic reaction because the patients’ chest pain attacks occurred immediately after the intravenous administration of corticosteroids and were accompanied by symptoms, such as urticaria and bronchial spasms. This type of allergic angina is sometimes referred to as “Kounis syndrome” (10). In our cases, however, other mechanisms inducing coronary vasospasms should be considered because our patients did not exhibit any characteristic symptoms of an allergic reaction. Conducting detailed investigations is necessary to clarify the exact mechanisms involved in the onset of corticosteroid-induced vasospastic angina.

With respect to treatment, we administered both calcium channel blockers and statins in our three cases because the patients had hypercholesterolemia. It is well known that statins have cholesterol-independent or “pleiotropic” effects, including improving endothelial dysfunction, inhibiting inflammatory responses and stabilizing atherosclerotic plaque, and are therefore beneficial in the treatment and prevention of atherosclerotic cardiovascular diseases (11). Furthermore, a previous study by Yasue et al. showed that statins are effective in suppressing the development of vasospastic angina (12). Our patients experienced no further anginal attacks after starting statin medications, suggesting that the addition of statins to calcium channel blockers is useful for controlling coronary spasms, as reported by Yasue et al.

Although reports of the occurrence of coronary vasospasms following the initiation of corticosteroid therapy are rare, it is possible that the frequency of corticosteroid-induced vasospastic angina is underestimated for various reasons, including misdiagnosis. For example, the symptoms of vasospastic angina may be confused with those of epigastric discomfort or epigastralgia associated with gastrointestinal side effects of corticosteroids. When corticosteroid therapy is initiated, clinicians should pay attention to the possible occurrence of vasospastic angina.

The authors state that they have no Conflict of Interest (COI).

References

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