CASE REPORT

Painful Left Bundle Branch Block Syndrome Complicated by Iron-Overload Cardiomyopathy

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Abstract:

Painful left bundle branch block (LBBB) syndrome is a rare disease that presents as simultaneous chest pain and transient LBBB without myocardial ischemia. We diagnosed a 72-year-old Japanese man with painful LBBB syndrome complicated by iron-overload cardiomyopathy. Phlebotomy was initially performed to improve myocardial iron deposition and conductive disturbance. Ironically, his chest pain was fully improved by the completion of incessant LBBB and walk-through phenomenon. However, this case demonstrates a clinically significant therapeutic strategy for cardiomyopathy-induced painful LBBB syndrome. Due to the lack of treatment guidelines, individualized treatment is required for each case of painful LBBB.

Key words: painful left bundle branch block syndrome, iron-overload cardiomyopathy

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Introduction

Painful left bundle branch block (LBBB) syndrome is a rare disease that presents as simultaneous chest pain, due to aberrant ventricular conduction, and transient LBBB without myocardial ischemia (1). Its exact pathophysiology remains unclear, and there are no established treatment guidelines. Meanwhile, iron-overload cardiomyopathy is also an uncommon disease caused by hemochromatosis, which leads to heart failure and arrhythmias, including conductive disturbance (2-4).

We herein present a case of painful LBBB syndrome complicated by iron-overload cardiomyopathy.

Case Report

A 72-year-old Japanese man with a history of hemochromatosis and unstable angina pectoris was brought to the emergency room due to transient chest pain at rest. Three years previously, he had been diagnosed with hemochromatosis, and phlebotomy treatment was initiated. Hereditary hemochromatosis was suspected, as he had no history of ineffective erythropoiesis, blood transfusion, ferrotherapy, or heavy alcohol consumption. However, the cause remained unclear because he refused to undergo a genetic analysis. The phlebotomy was continued for 15 months until his liver iron deposition, which was identified based on the examination of a liver biopsy specimen and magnetic resonance imaging, improved (Fig. 1A-D, Table 1). One year prior to his current presentation, he underwent percutaneous coronary intervention (PCI) using a paclitaxel-coated balloon (Sequent Please® 2.5 mm/15 mm, B. Braun Melsungen AG, Berlin, Germany) for 75% stenosis of his left circumflex coronary artery. However, even after PCI, he continued to experience occasional transient chest pain.

A physical examination revealed a blood pressure of 153/92 mmHg and no cardiac murmur. A 12-lead electrocardiogram showed normal sinus rhythm with a rate of 85 bpm without ST-segment change. However, the electrocardiogram temporally changed to sinus rhythm with complete LBBB coinciding with the abrupt onset of chest pain. The symptoms disappeared at the same time as the LBBB resolved (Fig. 2A-C). There were no changes in the electrocardiograms before and after chest pain. Echocardiography revealed normal left ventricular (LV) wall motion (Fig. 3A, B). The LV ejection fraction was 65%.

Due to the development of new LBBB, emergency coro-
Figure 1. Histological findings and magnetic resonance imaging suggesting liver iron deposition. The histological examination of a liver biopsy specimen revealed diffuse blue deposits of intracellular iron [original magnification (A) ×20 and (B) ×200, Berlin blue staining]. T1-weighted magnetic resonance imaging of the liver acquired using a 1.5 Tesla scanner (C) at the time of the diagnosis of hemochromatosis and (D) after the first 15 months of phlebotomy, illustrating improvement of iron deposition; the liver is not as dark as it appears in (C).

Table 1. Changes in Laboratory and Cardiac Magnetic Resonance Imaging Data over Time.

| Variables                              | First phlebotomy | PCI treatment | Baseline | Second phlebotomy |
|----------------------------------------|------------------|---------------|----------|-------------------|
|                                        | before           | after         | -17 months | 0 month | 6 months | 12 months |
| Laboratory values                      |                  |               |           |        |        |           |
| Ferritin [ng/mL]                       | 3,781            | 255           | 371       | 493    | 51      | 45        |
| Serum iron [μg/dL]                     | 264              | 79            | 109       | 163    | 118     | 69        |
| Transferrin [μg/dL]                    | 293              | 322           | 339       | 282    | 362     | 405       |
| Transferrin saturation [%]             | 90.1             | 24.5          | 32.2      | 57.8   | 32.6    | 17.0      |
| Hemoglobin [g/dL]                      | 17.7             | 14.0          | 16.8      | 17.7   | 14.7    | 14.7      |
| Albumin [g/L]                          | 4.1              | 4.0           | 4.4       | 4.5    | 4.4     | 4.1       |
| Cardiac magnetic resonance             |                  |               |           |        |        |           |
| LVEF [%]                               | 53               | 52            |           |        |        |           |
| LVEDV index [mL/m2]                    | 42.4             | 44.0          |           |        |        |           |
| LVM index [g/m2]                       | 42.6             | 45.4          |           |        |        |           |
| Mean T2* relaxation time (3.0 Tesla)   |                  |               |           |        |        |           |
| Global [ms]                            | 17.9             | 15.0          |           |        |        |           |
| Interventricular septum [ms]           | 6.5              | 5.0           |           |        |        |           |
| LV anterior wall [ms]                  | 18.6             | 18.1          |           |        |        |           |
| LV lateral wall [ms]                   | 25.6             | 15.7          |           |        |        |           |
| LV inferior wall [ms]                  | 20.7             | 21.1          |           |        |        |           |

LV: left ventricle, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVM: left ventricular mass, PCI: percutaneous coronary intervention
Figure 2. Electrocardiography. (A) Resting electrocardiographic monitor in lead II at the emergency room showing transient complete left bundle branch block (LBBB) simultaneously with abrupt chest pain, (B) 12-lead electrocardiography at baseline, (C) 12-lead electrocardiography at the time of transient complete LBBB with chest pain, and (D) 12-lead electrocardiography at spasm provocation test after the intra-coronary injection of acetylcholine.

A coronary angiography was performed; however, no significant stenosis was detected (Fig. 4A-C). Since there were no signs of myocardial ischemia, he was diagnosed with painful LBBB syndrome. A coronary artery spasm provocation test using an intra-coronary injection of acetylcholine (ACh) was performed. During a right ventricular (RV) temporary pacing test, chest pain occurred simultaneously with premature ventricular contraction or RV apex pacing. After an injection of 20 μg of ACh into the left coronary artery, a diffuse severe coronary artery spasm occurred with chest pain that was stronger than usual (Fig. 4D). Although a 12-lead electrocardiogram revealed T wave inversions in leads I, aVL, and V2-6, there was no LBBB development (Fig. 2D). The decreased flow-mediated dilatation (FMD) percentage (2.4%) suggested an impaired arterial endothelial function.

An exercise stress test did not provoke the development of LBBB. Due to his heart rate independent transient LBBB, and history of hemochromatosis, we suspected his LBBB to be caused by iron-overload cardiomyopathy. T2*-weighted cardiac magnetic resonance (CMR) imaging using a 3.0 Tesla scanner (Ingenia®, Philips, Eindhoven, Netherlands) revealed iron deposition in the myocardium. Since the T2* relaxation time was reduced, especially in the interventricular septum (6.5 ms, Fig. 3C, Table 1), we considered that the transient LBBB was caused by myocardial conductive disturbance due to iron deposition. Thus, phlebotomy treatment was restarted to treat iron-overload cardiomyopathy and painful LBBB syndrome.

Phlebotomy treatment was continued to maintain a ferritin level of <50 ng/mL (Table 1). After three months, his chest pain was relieved, but it was because his LBBB became incessant. A year later, CMR showed further shortening of the T2* relaxation time in the interventricular septum (5.0 ms, Fig. 3D, Table 1). Phlebotomy treatment could not prevent the progression of myocardial iron deposition and conductive disturbance. However, a coronary artery spasm provocation test and FMD test suggested an improvement in the endothelial function. Even upon the injection of the maximum doses of ACh, 50 μg and 100 μg for the right and left coronary arteries, respectively, significant coronary artery spasm was not provoked (Fig. 4E, F). The FMD percentage was increased to 13.0%. The patient has remained healthy without experiencing heart failure.

Discussion

Painful LBBB syndrome was first described in 1976 (5). Shvilkin et al. established the diagnostic criteria for painful LBBB syndrome (Table 2) in 2016 (1). The present case fulfilled all of the criteria. Although the pathophysiology of painful LBBB syndrome remains unclear, the dysynchronous ventricular contraction was considered as the cause of chest pain, possibly in combination with vascular endothelial dysfunction and vasospasm (6). Thus, biventricular pacing
After 12 months and His bundle pacing are effective in several cases (7-9). In cases with heart rate-dependent painful LBBB, heart rate control using β-blockers is effective (10, 11). However, in our case, the patient expressed reluctance towards pacing treatment due to pain experienced when temporary RV apex pacing was performed. Furthermore, his transient LBBB was not heart rate dependent. Rather, it was caused by iron overload in the myocardium.

Hemochromatosis, introduced by von Recklinghausen in 1889 (12), refers to the clinical disorder caused by excess total body iron with organ failure due to iron toxicity. Iron-overload cardiomyopathy, a major organ failure caused by hemochromatosis, is a potentially reversible myocardial dysfunction, effective treatments for which include phlebotomy and iron chelation therapy (13, 14). Thus, we attempted to treat the patient with phlebotomy, aiming to improve the myocardial iron deposition and conductive disturbance.

Although we believed that phlebotomy treatment had a potential to improve the patient’s chest pain due to the disappearance of transient LBBB, this was not realized despite restarting phlebotomy in accordance with the recommended protocol (15). Since the myocardial iron deposition had already progressed, it was too late to improve the myocardial conductive disturbance. Ironically, the symptoms were resolved by the completion of incessant LBBB and walk-through phenomenon: the patient became accustomed to dysynchronous ventricular contraction (1, 11). However, this case demonstrates a clinically significant therapeutic strategy for cardiomyopathy-induced painful LBBB syndrome. In patients with painful transient LBBB due to a potentially reversible cardiomyopathy, the optimal treatment for the myocardial injury should be considered first. If it is not effective, chest pain resolution due to pacing treatment as a second therapeutic option or the walk-through phenomenon secondary to myocardial conductive disturbance progression is expected.

Measurement of the T2* relaxation time on CMR is an established method for evaluating myocardial iron concen-

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**Figure 3.** Echocardiography and cardiac magnetic resonance imaging. End-diastolic and -systolic (A) short axis view and (B) 4-chamber view at baseline revealed normal left ventricular wall motion and thickness. T2*-weighted images of the short-axis myocardium acquired by 3.0 Tesla magnetic resonance imaging (C) at baseline and (D) 12 months after starting the second phlebotomy treatment are shown. In both (C) and (D), the shortening of the T2* relaxation time is depicted as dark blue color especially in the interventricular septum (red arrows), which suggests partial myocardial iron deposition.
A previous report suggested that thalassemia patients with T2* relaxation times of <10 ms and <20 ms calculated from a 1.5 Tesla CMR scan had significantly increased risk of developing heart failure and arrhythmia, respectively (16). These cut-off values were equivalent to T2* relaxation times of <5.8 ms and <12.6 ms, respectively, calculated from a 3.0 Tesla CMR scan (17). In the present case, severe myocardial deposition was only observed in the interventricular septum. Thus, we considered that the patient’s first phlebotomy treatment was partially effective for improving the myocardial iron deposition, and that it should have been continued. In cases with hemochromatosis, CMR management and consecutive phlebotomy treatment are needed to prevent cardiovascular disorders.

An impaired endothelial function was also considered as a result of iron deposition to the vasculature and one of the factors of painful LBBB syndrome. Gaenzer et al. reported that endothelial dysfunction was caused by oxidative stress due to iron overload, and it may be alleviated by phlebotomy (18). The result of the spasm provocation test one year after starting the second phlebotomy treatment suggested an improvement in the coronary artery endothelial function, and this may have contributed to the resolution of painful LBBB syndrome.

**Conclusion**

We reported the case of a patient with painful LBBB syndrome, complicated by iron-overload cardiomyopathy. In

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**Table 2. Diagnostic Criteria for Painful LBBB Syndrome Established by Shvilkin et al. Reference (1).**

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|---|---|
| 1 | Abrupt onset of chest pain coinciding with the development of LBBB |
| 2 | Simultaneous resolution of symptoms with resolution of LBBB (although occasionally a walk-through phenomenon may be present) |
| 3 | Normal 12-lead electrocardiograms before and after LBBB (occasionally T wave inversions may be present with morphology pattern consistent with that of T wave memory) |
| 4 | Absence of myocardial ischemia during functional stress testing |
| 5 | Normal left ventricular function and the absence of other abnormalities to explain symptoms |
| 6 | Low precordial S/T wave ratio consistent with new-onset LBBB (<1.8 in this series) and inferior QRS axis |

LBBB: left bundle branch block

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**Figure 4.** Coronary artery angiography. Coronary artery angiograms at the baseline of (A) RCA and (B, C) LCA are shown. An LCA spasm provoked after the intra-coronary injection of 20 μg of ACh at baseline is presented in (D). After 12 months, significant coronary artery spasm was not provoked following the intra-coronary injection of 50 μg and 100 μg of ACh into (E) the RCA and (F) LCA, respectively. ACh: acetylcholine, CAU: caudal, CRA: cranial, LAO: left anterior oblique, LCA: left coronary artery, RCA: right coronary artery
cases involving chest pain with new-onset LBBB, acute coronary syndrome should be distinguished. If myocardial ischemia is ruled out, painful LBBB syndrome should be considered, and its cause should be investigated. The treatment of painful LBBB syndrome should be individualized according to the cause.

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

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