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Subacute Stent Thrombosis Associated With a Heparin-Coated Stent and Heparin-Induced Thrombocytopenia

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Subacute stent thrombosis occurred in a patient 34 days after receiving a heparin-coated (HC) stent. The patient developed heparin-induced thrombocytopenia and diffuse thrombosis after the stent was placed. This raises the concern that patients who develop heparin-associated antibodies in the context of a recently placed HC stent may have an increased risk for subacute stent thrombosis. *Cathet Cardiovasc Intervent 2003;58:80–83.* © 2003 Wiley-Liss, Inc.

Key words: subacute thrombosis; heparin-induced thrombocytopenia; heparin-coated stent

INTRODUCTION

The incidence of subacute thrombosis in heparin-coated (HC) stents is rare even in the setting of myocardial infarction. This is the first reported case of subacute thrombosis of an HC stent that occurred in the setting of heparin-induced thrombocytopenia and thrombosis (HITT). The management of this patient and a brief discussion of HITT are presented.

CASE REPORT

A 66-year-old man presented to the emergency room with 15–20 mm ST elevations in the inferior leads and brisk, lower gastrointestinal (GI) diverticular bleeding. He was taken to the catheterization laboratory where a 4.5 mm diameter RCA was opened with a Velocity 4 mm × 18 mm HC stent (Fig. 1). The HC stent was chosen to minimize the need for systemic anticoagulation in the setting of a GI bleed. Six units of packed red blood cells were transfused before bleeding subsided. Clopidogrel was initiated immediately after stent deployment, but aspirin was not given. Abciximab was initially started in the catheterization laboratory due to distal embolization of the clot. However, this was discontinued after 2 hr because of subsequent hematemesis. Repeat catheterization 1 day after stenting revealed a patent RCA. Left ventricular ejection fraction was 45%. The hospital course was unremarkable except for new onset of paroxysmal atrial fibrillation, which resolved in less than 24 hr. He was discharged on hospital day 6 in stable condition on clopidogrel, aspirin, and amiodarone.

Fifteen days after stent placement, the patient developed acute onset of right hemiparesis and expressive aphasia. Magnetic resonance imaging (MRI) demonstrated multiple infarcts in the left middle cerebral artery territory. Magnetic resonance angiogram did not reveal stenosis in the carotid or cerebral vessels. The event was presumed to be cardioembolic. The patient was continued on clopidogrel and heparin was initiated. Aspirin was held to minimize the risk of hemorrhagic conversion of the stroke. Repeat MRI on hospital day (HD) 2 revealed evidence of a new stroke despite therapeutic levels of heparin. Doppler ultrasound showed extensive bilateral, common femoral venous thrombosis. Echocardiography demonstrated a patent foramen ovale without LV aneurysm or clot. The platelet count decreased from 413,000 at the time of discharge from the previous admission for myocardial infarction to 130,000 on the second admission, to 96,000 on HD 2 and 51,000 by HD 4. Heparin-associated antibody assay was positive. A diagnosis of

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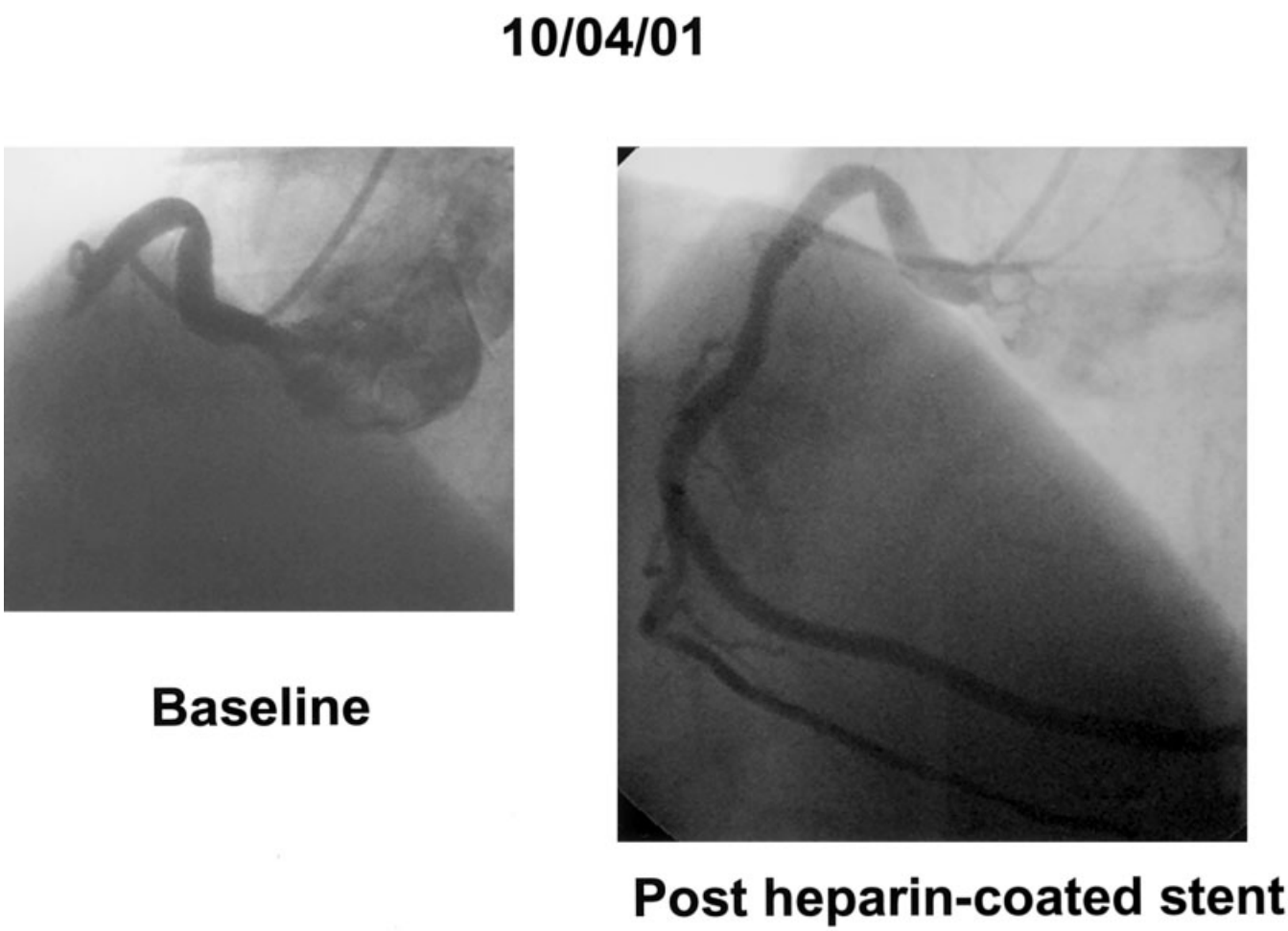

Fig. 1. Angiogram showing proximal thrombosis of the right coronary artery (left) and the final result after placement of heparin coated stent (right).

HITT was made. Heparin was discontinued on HD 3 and an inferior vena cava filter was placed. A work-up for a hypercoagulable state was negative and underlying malignancy was not identified.

The source of stroke was unclear; the etiologies considered included the following. First, intracardiac thrombus. The patient had a recent inferior wall myocardial infarction and one episode of intermittent atrial fibrillation. Transthoracic echo did not reveal a thrombus, and transesophageal echocardiogram could not be performed because of poor patient cooperation. Second, paradoxical stroke in the setting of patent foramen ovale and deep vein thrombosis (DVT). And third, HITT syndrome with in situ cerebral thrombosis and DVT. Consistent with this, the platelet count returned to baseline upon cessation of intravenous heparin. The patient was placed on argatroban and clopidogrel. Altered mental status resolved by HD 6 and motor function and expressive aphasia continued to improve with rehabilitation. The patient was continued on coumadin for paroxysmal atrial fibrillation and for deep venous thrombosis. Clopidogrel was continued for 4 weeks after stent placement.

Thirty-four days after stent placement, the patient developed severe chest pain. Electrocardiogram showed acute ST elevations of 3–4 mm in the inferior leads. This occurred while the patient was therapeutic on coumadin (INR = 2.1) and only 3 days after clopidogrel was discontinued. He was given aspirin, clopidogrel, and argatroban and taken to the catheterization laboratory. Before the start of the procedure, the patient developed recurrent episodes of ventricular fibrillation requiring resuscitation with multiple doses of epinephrine, amiodarone, and repeated defibrillation. He was treated for approximately 45 min before a stable rhythm was established with the use of a transvenous pacemaker. Blood pressure was supported with an intra-aortic balloon pump and epinephrine drip. Angiography demonstrated complete occlusion of the proximal right coronary artery (Fig. 2). A 3.0 $\times$ 20 mm balloon was inflated with restoration of blood flow through the right coronary

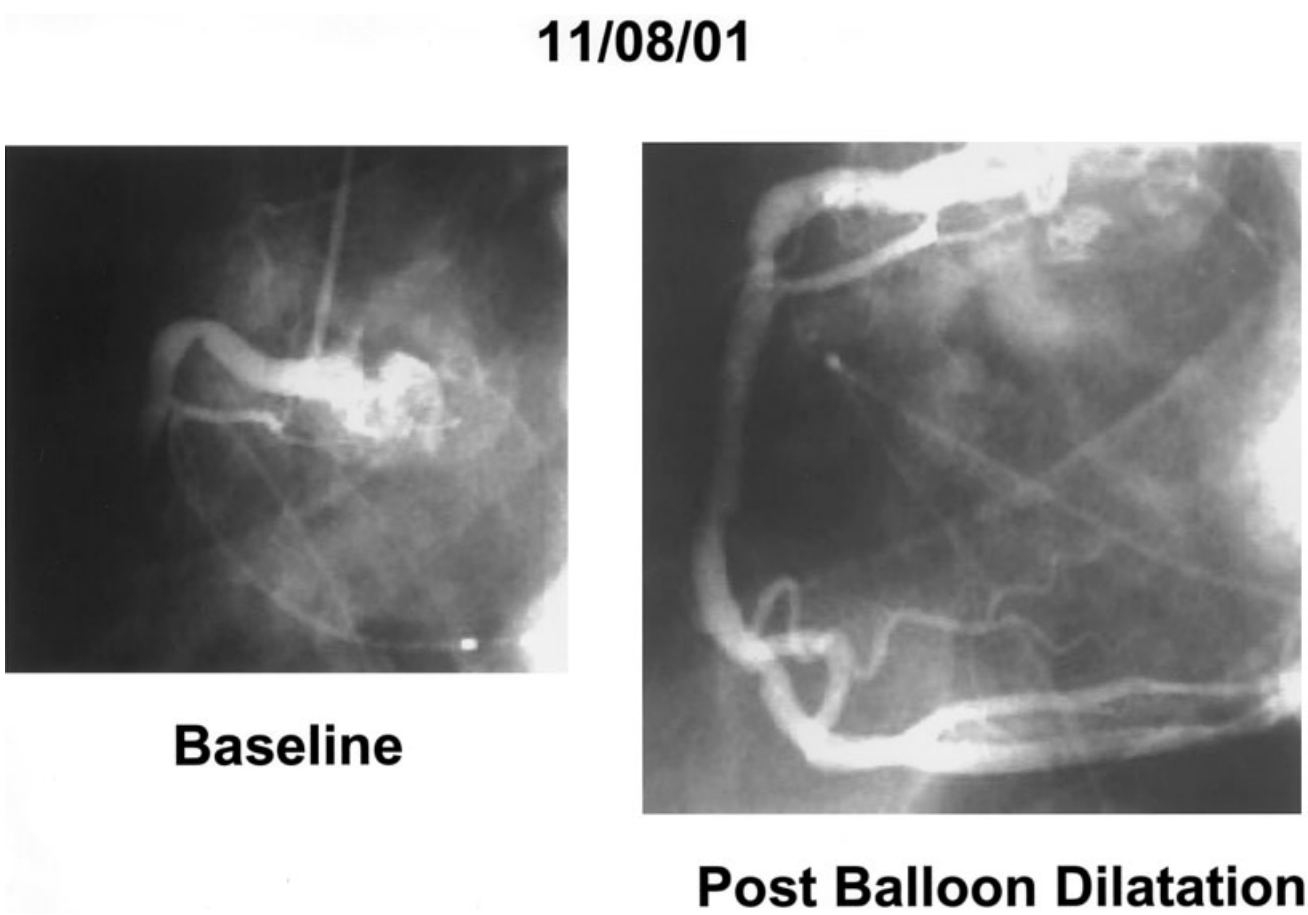

Fig. 2. Angiogram showing subacute thrombosis of the heparin-coated stent 34 days after placement (left) and the final result after balloon angioplasty (right).

artery system. Once flow was established, vital signs stabilized and he was weaned off epinephrine and balloon pump over the next 48 hr. He returned to baseline neurologic status despite the prolonged resuscitation. He was maintained on aspirin, clopidogrel, and coumadin and remained clinically free of repeat thrombotic episodes 4 months after repeat PTCA of the RCA.

DISCUSSION

Heparin-induced thrombocytopenia (HIT) occurs in 5%–10% of patients treated with heparin [1]. It can occur when administered via subcutaneous or intravenous route, or even when heparin-coated catheters are utilized [2]. HITT occurs in 10%–20% of patients that develop HIT and has a 30% mortality rate [1]. In these syndromes, heparin and platelet factor 4 form a complex that induces heparin-associated immunoglobulin G (IgG) [3]. Platelets in HIT have increased surface expression of Fc receptor, which binds to the Fc region of IgG. The heparin-associated antibodies (HAAbs) therefore result in enhanced platelet aggregation by the Fc receptor/HAAbs interaction. In addition, HAAbs activate platelets to release procoagulant factors, such as thromboxane A2. The tendency for platelet aggregation leads to "white" or platelet clots, which manifest as arterial and venous thrombosis such as myocardial infarction, stroke, limb ischemia, or, most commonly, deep venous thrombosis.

HC stents have been used clinically with a low incidence (0.14%–0.8%) of subacute thrombosis [4,5], even in patients with acute MI [6]. According to the manufacturer, this is the first report of HC stent thrombosis in a patient with HIT. The purified heparin bound to the stent (approximately 1 unit heparin/stent) is metabolically active until the struts are covered by tissue. The large size of the stented vessel in our patient would make spontaneous subacute thrombosis unlikely. Because the platelet count fell rapidly from 413,000 to 130,000 in the presence of only the HC stent, we postulate that the heparin coating maintained the stimulation for HAAb formation that evolved into the presentation of HITT. The intravenous heparin administered on admission for the stroke

may have exacerbated this condition, leading to further thrombocytopenia and an additional stroke. Even if the HC stent did not induce the HITT, the presence of an HC stent in a patient who subsequently develops HIT likely predisposed this individual to subacute stent thrombosis. Consistent with this, HC stents have been demonstrated to cause platelet aggregation in vitro in the presence of heparin-induced antibodies [7]. Furthermore, thrombosis of arterial conduits is more likely to occur in patients with heparin-associated antibodies [8].

The treatment of HIT and HITT involves immediate cessation of all sources of heparin. Coumadin should not be started in the early stages of HIT since this can worsen thrombosis by depleting proteins C and S [9]. Coumadin can be safely initiated after resolution of thrombocytopenia. Alternatives to heparin include direct thrombin inhibitors such as argatroban, which has been demonstrated to reduce further thrombotic events in HITT [10]. Plasma exchange, in combination with antiplatelet agents, has also been used effectively [11]. Blocking thromboxane release by using aspirin is not sufficient for preventing platelet aggregation [12], but abciximab has been demonstrated to prevent aggregation in the presence of HAAbs in vitro [13]. In this patient, a combination of argatroban with subsequent conversion to coumadin, along with clopidogrel, was used. It is of interest that the subacute thrombosis of the stent occurred 3 days after the discontinuation of the clopidogrel despite a therapeutic coumadin level. Therefore, when treating patients with HC stents who subsequently develop HIT, it may be judicious to continue aggressive antiplatelet therapy with thienopyridines and aspirin in addition to coumadin. This therapy should be continued until the heparin-bound struts are completely covered by tissue.

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