Vasculitis resulting from a superficial femoral artery angioplasty with a paclitaxel-eluting balloon

Shannon D. Thomas, FRACS,[a] Robert R. A. McDonald, FACD,[b,c] and **Ramon L. Varcoe, MS, FRACS,[a,d,e]**
Sydney, New South Wales, Australia

Drug-eluting balloons (DEBs) coated with the antiproliferative agent paclitaxel may improve primary patency by reducing recurrent luminal stenosis. A proportion of the active drug and excipient coating are known to embolize distally, but until now, there have been no reports of adverse events resulting from their use. We report an unusual case of a painful nodular, biopsy specimen-proven vasculitic rash that afflicted the ipsilateral lower limb of a patient after superficial femoral artery treatment with a DEB. This adverse event may have implications for the use of DEB in this and other vascular territories. (J Vasc Surg 2014;59:520-3.)

Drug-eluting balloons (DEBs) are effective at reducing intimal hyperplasia after angioplasty of the superficial femoral artery, infrapopliteal circulation, and arteriovenous fistulas.[1-4] As a tool to both prevent and treat restenosis, DEBs are being applied to an ever-broader variety of vascular territories, including the carotid and coronary arteries.[5-7] Until now, there have been no reports of target organ vasculitic, allergic, or hypersensitivity reactions with the use of this device.

CASE REPORT

A 72-year-old woman presented to our institution with a progressive 1-month history of severely restrictive recurrent left leg claudication. Before presentation, her left leg had been asymptomatic for 9 months after undergoing bare-metal stent revascularization of the midsuperficial femoral artery. Examination revealed palpable bilateral femoral pulses but absent popliteal and pedal pulses on the symptomatic side. Her limbs showed no evidence of venous disease, rash, or ulceration. Arterial duplex ultrasound imaging revealed a critical in-stent stenosis of the previously placed superficial femoral artery stent (peak systolic velocity, 438 cm/s) with a reduced ankle-brachial pressure index of 0.75.

She had a history of dyslipidemia and hypertension, with known allergies to rosuvastatin (skin rash) and ezetimibe (skin rash). She was receiving lipid-lowering (gemfibrozil), antihypertensive (ramipril), and dual-antiplatelet (clopidogrel and aspirin) medications.

From the Department of Surgery, Prince of Wales Hospital[a]; Sky Blue Dermatology[b]; the Department of Dermatology, St. Vincent's Hospital[c]; the Faculty of Medicine, University of New South Wales[d]; and The Vascular Institute, Prince of Wales Hospital.[e]

Author conflict of interest: Dr Thomas has been given an educational grant by Medtronic Endovascular.

Reprint requests: Dr Ramon L. Varcoe, Prince of Wales Private Hospital, Barker St, Ste 8 Level 7, Randwick, NSW 2031, Australia (e-mail: r.varcoe@unsw.edu.au).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2013.03.013

The patient underwent an elective superficial femoral artery angioplasty procedure. The lesion was approached through an atraumatic antegrade left common femoral artery puncture and placement of a 6F Britetip sheath (Cordis, Johnson & Johnson, Warren, NJ). After predilatation with a 6- × 100-mm conventional Fox Cross balloon catheter (Abbott Vascular, Abbott Park, Ill), a 6- × 120-mm In.Pact Admiral DEB, with paclitaxel coating (3 μg/mm^2; Invatec, Medtronic, Minn) was inflated according to the manufacturer's recommendation. Completion angiography demonstrated a pleasing angiographic result, free of dissection, recoil, or thrombus. No evidence of distal embolization was apparent on runoff angiography. There were strong popliteal and pedal pulses after the procedure, and she was discharged the next day with no evidence of rash.

She presented 1 week after the procedure after developing a mildly painful rash, prominent on the distal aspect of her left lower limb from the lower thigh to the ankle but which spared the foot (Fig 1). The rash consisted of nonblanching, small erythematous nodules that were nonhemorrhagic. No additional cutaneous lesions were noted on her body.

Analysis of a punch biopsy specimen showed epidermal and upper dermal edema with an intense inflammation of the medium-sized vessels in the superficial subcutaneous fat. Prominent fibrin deposition and a mononuclear infiltrate within the arteriole walls was noted, as well as thrombosis of surrounding small vessels and a diffuse infiltrate containing neutrophils and eosinophils (Fig 2). The result of a vasculitic blood screen was negative for the presence of an underlying systemic vasculitis syndrome. In view of the histopathologic analysis, the distribution of the rash, and its temporal relationship to the procedure, a diagnosis of vasculitis secondary to the DEB was made.

The patient was treated with a short course of oral steroids and emulsifying ointment. During the next 12 weeks, the rash continued to improve but did not completely resolve. Pain and itch have since abated, and no serious adverse event has eventuated at 4 months of follow-up.

DISCUSSION

The current commercially available DEBs all use the antiproliferative drug paclitaxel to prevent or treat restenosis after the successful dilatation of an arterial stenosis. This

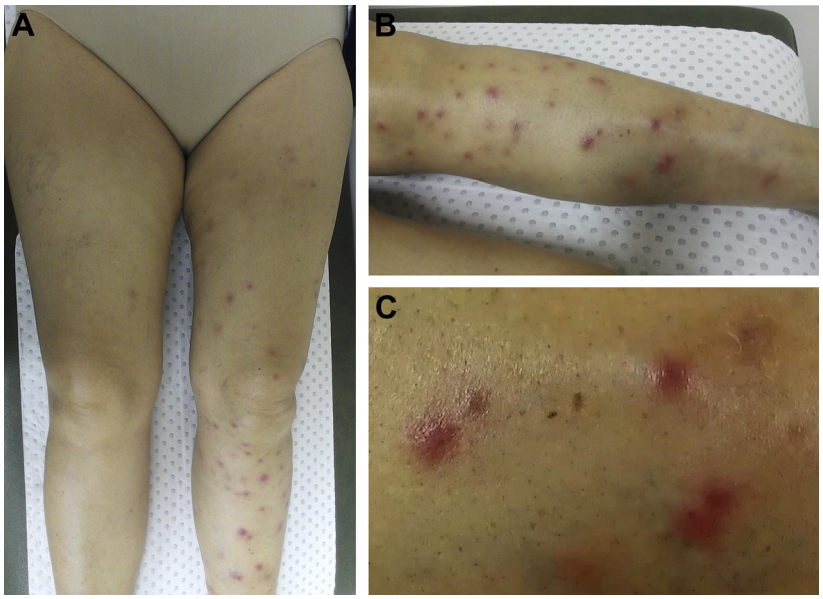

Fig 1. A, Vasculitic rash confined to the left leg after therapy with a paclitaxel-eluting balloon. **B,** Nodular, erythematous macules in the distribution of the superficial femoral artery treated with a paclitaxel-eluting balloon. **C,** Magnified view of the vasculitic rash on the lower leg, demonstrating nonblanching, nonhemorrhagic, nodular, erythematous macules.

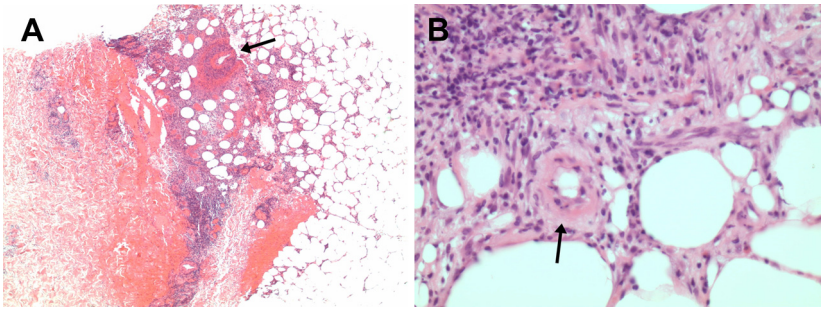

Fig 2. A, Photomicrograph (original magnification, ×40) of histologic specimen demonstrates inflammation and fibrin within the wall of an arteriole within the subcutaneous fat (*arrow*). **B,** Photomicrograph (original magnification, ×400) shows mixed cellular infiltrate comprising lymphocytes, neutrophils, and eosinophils in the subcutis and a thrombosed small vessel with fibrin within its wall (*arrow*).

highly lipophilic drug[8] inhibits the proliferation of vascular smooth muscle cells that would otherwise accumulate within the neointima and form a hyperplastic restenotic lesion.[9] A variety of excipient carrier molecules have been used to facilitate paclitaxel delivery to the target lesion, including urea, iopromide, butyryl-tri-hexyl citrate, and shellolic acid.[10] During balloon inflation, these drugs are liberated, some implanting as drug reservoirs into the blood vessel wall to exert their effect locally, whereas other clumps are released downstream in a phenomena known as "particulate embolization." This phenomenon was studied by Heilmann et al[11] in a porcine model, in which they demonstrated that >50% of the drug coating washes off into the distal circulation. In that study, the type of excipient and method of balloon coating (drug-coated or wrapped) affected the efficiency of drug transfer. In human studies, Freyhardt et al[12] demonstrated paclitaxel within the systemic circulation after lower limb DEB angioplasty. There is concern about what long-term effect this shower of drug into the end organ may have; however to date, there have been no published reports of allergy or vasculitic reactions. This has been reassuring for all who use these devices and has resulted in their broad application to include vascular territories where the end organ may be less forgiving than the lower limb.[10,13]

We propose that our patient's vasculitic rash was related to particulate embolization of the drug coatings on the balloon, of which paclitaxel and urea feature most prominently. In support of this, we note that the rash was present only in the vascular territory fed by the treated superficial femoral artery and appeared 5 days after that treatment. Close physical examination of her skin and