Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

A spontaneous coronary arterial dissection associated with a calcineurin inhibitor

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Summary

We present the case of a 55-year-old lady presenting 5 months after a liver transplant with acute coronary syndrome. She was on maintenance-dose tacrolimus. An angiogram diagnosed a spontaneous coronary artery dissection, which was successfully stented. This is the third case in the literature associating a calcineurin inhibitor with a spontaneous coronary arterial dissection. The detrimental effect of calcineurin inhibitors on vasculature is well recognised. This report highlights their potentially serious side-effects. It should be appreciated that calcineurin inhibitors have the potential to cause or contribute to this rare vascular phenomenon and the diagnosis should therefore be considered in those taking such drugs.

BACKGROUND

We present the first case of a spontaneous coronary artery dissection (SCAD) in a patient on the calcineurin inhibitor, tacrolimus. To date, there have been two cases of arterial dissection associated with ciclosporin, the prototypical calcineurin inhibitor. Calcineurin inhibitors have a well-documented detrimental effect on vasculature; this report highlights their potentially serious vascular side-effects calcineurin inhibitors.

CASE PRESENTATION

A 55-year-old woman had a successful cadaveric orthotopic liver transplant in 2010 for a cross-over syndrome of primary sclerosing cholangitis and autoimmune hepatitis. She was stable on a maintenance regimen of prednisolone 15 mg once daily and tacrolimus 5 mg twice daily. Other than her liver disease, she had no other significant medical history; in particular she had no history of connective tissue disorders such as Ehlers-Danlos syndrome.

Five months after her transplant, she presented to the hospital after awakening from her sleep with severe chest pain radiating to her right shoulder.

On arrival, her heart rate was 75 beats per minute with a blood pressure of 158/86 mm Hg and an oxygen saturation of 98% on air. Clinical examination was unremarkable. Her ECG showed sinus rhythm with ST elevation in I, aVL, V2 and V3 and ST depression in II, III, V4, V5 and V6. D-dimer was normal while troponin T was raised at 404 ng/l (normal range <14 ng/l). The tacrolimus level was 14.4 ng/ml (therapeutic dose <20 ng/ml).

She underwent immediate angiography while symptomatic, which revealed unobstructed coronary arteries with minimal atherosclerotic disease. Ventricular function was normal. She was started on aspirin, pravastatin, ramipril and bisoprolol. She was diagnosed with atypical chest

pain and as she was asymptomatic she was discharged later than day.

Unfortunately, later that night an identical pain recurred, for which she was readmitted to the hospital.

INVESTIGATIONS

Her ECG changes were similar with widespread ST depression. Her troponin was 2169 ng/l (normal range <14 ng/l). A second angiogram revealed a coronary arterial dissection in the left anterior descending artery that was obstructed (figure 1A).

TREATMENT

The lesion was stented with an endeavour 2.5×30 mm drug-eluting stent with a good angiographic result (figure 1B). The patient had mild chest pain for a few days after stent insertion. A third angiogram was undertaken to exclude stent migration or a persistent dissection. This angiogram was normal and the chest pain was therefore attributed to occlusion of minor side branches by the stent.

OUTCOME AND FOLLOW-UP

Thereafter, an uncomplicated recovery was made and the patient was discharged after 4 days. The patient remained systemically well with normal exercise tolerance 1 year after. Her most recent echocardiogram showed good left ventricular function with no regional wall motion abnormalities.

DISCUSSION

Spontaneous coronary artery dissection

SCAD is a rare cause of acute coronary syndrome. To date, there have been approximately 300 documented cases of SCAD. It is thought to cause 0.2–1.1% of cases of acute coronary syndrome.¹ A tear in the intima allows a

Figure 1 (A) Angiography demonstrating a proximal lesion of the left anterior descending (LAD) artery (arrow). Secondary obliteration of distal lumen is also observed. (B) Angiogram after stent insertion allowing restoration of the true lumen of the LAD.

haematoma to form within a false lumen, which, if there is compromise of the true lumen, results in distal ischaemia.

While there are many risk factors, most cases of SCAD remain idiopathic. In general, 70% of cases are of females, and of those, 30% are in the postpartum period. Other risk factors include connective tissue disorders (eg, Ehlers-Danlos syndrome), vasculitides, (eg, systemic lupus erythematosus), hypertension and strenuous exercise. Taken collectively, the aetiology is likely to be a combination of hormonal changes, haemodynamic changes and structural changes.

In contrast to ischaemic heart disease secondary to atherosclerosis, the mean age of SCAD presentation is 30–45.² The interaction between SCAD and atherosclerosis is not fully understood. On the one hand, atherosclerosis has been shown to physically limit the extension of a dissection. On the other hand, atherosclerotic plaque may rupture causing intimal damage that results in a dissection.^{3 4}

SCAD may present as unstable angina, myocardial ischaemia, cardiogenic shock or sudden death.⁵ Radiologically, intravascular ultrasound, coronary CT angiography and conventional angiography are all utilised methods of diagnosing SCAD.

Treatment may be conservative if the patient is asymptomatic and haemodynamically stable. Otherwise, percutaneous intervention is usually performed. If undetected, mortality is approximately 40%.⁶ However, once detected and treated, this falls to around 3%.¹ Prognosis is excellent and there is little risk of recurrence.

Vascular effects of calcineurin inhibitors

Calcineurin inhibitors brought significant improvements to graft survival. However, they have been shown to be detrimental to both donor and recipient vasculature. Kidney allografts exhibit two distinct patterns in the presence of calcineurin inhibitors (such as tacrolimus): acute arteriopathy and thrombotic microangiopathy.^{7–9}

Suggested mechanisms by which calcineurin inhibitors cause vascular phenomena are wide ranging. They have been shown to be a potent vasoconstrictor by altering the levels of the vasodilator nitric oxide and the

vasoconstrictor endothelin.⁹ Other proposed mechanisms of vascular pathology are increased production of reactive oxygen species,¹⁰ increased sympathetic tone¹¹ and change in balance between proinflammatory and anti-inflammatory cytokines.^{12–14}

Tacrolimus has been shown to be less aggravating to the vasculature by causing less inflammation and having fewer effects on vasoactive substances.^{9 11 15 16}

To date, there have been two case reports of patients post-transplant receiving ciclosporin therapy who have had SCAD.¹⁷ Both a 17-year-old boy and a 63-year-old man who had a renal transplant for polycystic kidney disease were diagnosed with SCAD on angiography and ultimately treated with coronary artery bypass grafting. Notably, as with our patient, both were on regular prednisolone. We are not aware of any other documented case of arterial dissection with tacrolimus. A potential cause of arterial dissection is trauma due to angiography. This was not considered to be the case due to the distal position of the dissection.

It is clear that calcineurin inhibitors as a class interact with vasculature and can contribute to vascular pathology. With this being only the third reported association with SCAD with a calcineurin inhibitors and the first with tacrolimus, causality cannot be definitely inferred. However, it should be appreciated that calcineurin inhibitors have the potential to cause or contribute to this rare vascular phenomenon.

Learning points

- ▶ Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome with high mortality.
- ▶ SCAD may be missed on early angiograms.
- ▶ The outcome in SCAD can be excellent if treated promptly with stenting.
- ▶ Tacrolimus and other calcineurin inhibitors may contribute to rare vascular phenomenon such as SCAD.
- ▶ Patients presenting with acute coronary syndrome on a combination of calcineurin inhibitor and prednisolone should have a diagnosis of SCAD considered.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Mallon DH, McKenzie D, Dayer M. A spontaneous coronary arterial dissection associated with a calcineurin inhibitor.

BMJ Case Reports 2012;10:1136/bcr-2012-006414, Published XXX

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