acid was added. She had a scan at 20 weeks that showed normal morphology and growth. At 18 and 32 weeks, fetal echocardiography was normal. At 22 weeks she developed severe arthralgia and lethargy, and her serology indicated an SLE flare (increasing double stranded DNA titres and falling levels of complement 3 and 4). She required 40 mg of prednisolone for symptom control. However, home blood glucose monitoring showed a raised blood glucose concentration, and gestational diabetes was confirmed with an oral glucose tolerance test. She required insulin four times a day in a basal bolus regimen until delivery. Prednisolone was reduced slowly to a 20 mg maintenance dose once daily.

Repeat growth scans were adequate, and labour was induced at 38 weeks for worsening arthralgia and hypertension. Urine analysis remained negative. A 2.5 kg live female infant was delivered vaginally, and the patient was discharged on day 3. The postnatal period was uncomplicated, and the mother breast fed her infant. She stopped insulin immediately after delivery, and antihypertensives were stopped 10 days later. Prophylactic low molecular weight heparin was prescribed postpartum for six weeks in view of the presence of anticardiolipin antibodies and SLE flare. Prednisolone was slowly reduced to 4 mg daily over three months.

Conclusion

Systemic lupus erythematosus and the overlap condition of the antiphospholipid syndrome present several challenges in managing a pregnant woman and her

fetus. A successful pregnancy outcome depends on stratification of risk at the outset (ideally before pregnancy) and careful and appropriate monitoring during the pregnancy. Should the disease flare up, aggressive but considered management is advocated to reduce maternal and fetal morbidity.

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LESSON OF THE WEEK

Anal ulceration induced by nicorandil

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In patients with anal fissures or anal ulceration, treatment with the drug nicorandil should be considered as a possible cause

Nicorandil is widely used to treat angina, particularly in patients with severe coronary vessel disease. Anal ulceration is a recognised side effect of its use,^{1 2} but the association between the two is not widely appreciated. We want to alert primary care practitioners, general physicians, dermatologists, cardiologists, and surgeons who may encounter such cases of the importance of this association.

Case report

A 73 year old man was referred to our department with a one year history of rectal bleeding, mucus discharge, and anal pain. Associated conditions included diabetes mellitus, hypertension, hypercholesterolaemia, and severe

ischaemic heart disease. Despite two previous coronary artery bypass operations, he continued to have angina. His medication included aspirin, atenolol, amlodipine, simvastatin, allopurinol, gliclazide, and 30 mg nicorandil twice a day.

Initial assessment found a small posterior anal fissure and anal skin tags. For investigation of the bleeding, he underwent a rigid sigmoidoscopy and a barium enema, results of which were normal. We made a provisional diagnosis of an uncomplicated idiopathic anal fissure and started him on conservative treatment with topical analgesics and laxatives.

His symptoms worsened, however, with increasing mucus discharge. Examination under anaesthesia showed normal rectal mucosa. There was a huge posterior anal fissure (2-3 cm wide) extending the entire length of the anal canal and another anterior fissure 1.0-1.5 cm wide with a flat base. The margins of the fissures were soft and non-indurated. We considered a diagnosis of Crohn's disease or malignancy, but

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Fig 1 Anterior fissure

Fig 2 Posterior fissure

histological examination of biopsy specimens from the lesion showed simple ulceration only.

We changed the treatment to chemical sphincterotomy with topical application of diltiazem gel 2% for two months and concentrated on tight glycaemic control. Despite this, the ulceration progressed. Addition of glycerine trinitrate ointment 0.2% also failed, as did additional treatment with ciprofloxacin and metronidazole. We undertook further investigations to identify unusual causes of anal ulceration but results were negative, including those for HIV, syphilis, chlamydia, and lymphogranuloma venereum. Magnetic resonance imaging of the perianal region showed a suspected anal fistula associated with the fissure and so we undertook another examination under anaesthesia. We did not find a fistula, but the ulceration had deepened and enlarged to 2–3 cm wide and was eroding into intersphincteric plane (figs 1 and 2).

At this stage we became aware of reports of anal ulceration associated with nicorandil. After consultation with a cardiologist, we stopped the nicorandil and substituted it with isosorbide mononitrate. This resulted in the patient having an immediate episode of severe angina, but he recovered well. When the patient was reviewed in clinic two months later, his anal symptoms had improved considerably and the ulcer had reduced in size by 75%. Further healing continues.

Discussion

Nicorandil, a nicotinamide ester, is a synthetic nicotine derivative that causes opening of potassium channels that are sensitive to adenosine triphosphate. It is widely used in patients with angina because its unique pharmacological actions increase blood flow in the coronary arteries and reduce cardiac preload and afterload.

Oral and intestinal ulceration caused by nicorandil are well documented side effects,³ but anal ulceration has only recently been reported.^{1 2 4 5} The pathogenesis is not clearly understood, but proposed theories include a direct effect of nicorandil or one of its metabolites on the anal mucosa or a vascular steal phenomenon.^{1 2 4}

The anal ulceration associated with nicorandil usually presents clinically with anal pain. Mucus discharge and rectal bleeding are less common. Anal ulceration usually occurs spontaneously but sometimes develops after anal trauma. Researchers have described three cases in which it developed after minor perianal surgery (two after exci-

sion of minor anal skin tags and one after drainage of a perianal abscess).^{5 6} Histological examination of biopsies from anal ulcers associated with nicorandil shows a non-specific inflammatory reaction with granulation tissue.⁷ Other causes of perianal ulceration—such as Crohn's disease, Wegener's granulomatosis, tuberculosis, HIV, herpes simplex, cytomegalovirus, syphilis, amoebiasis, lymphogranuloma venereum, lymphoma, acute myeloid leukaemia, and anal cancers (epidermoid and non-epidermoid)—should be excluded.

Our literature review suggests that most of the patients who developed anal ulceration associated with nicorandil were taking a dose of 30 mg twice a day, although ulceration at a lower dose has also been reported.^{1–12}

After withdrawal of nicorandil, ulcer healing may take place in as little as two weeks. In most cases it takes at least 12 weeks and in some cases up to six months. Surgical intervention does not help in the healing of these ulcers. There are reports of six patients having undergone diversion colostomies and one an abdominoperineal excision of the rectum.^{7 11} One patient is reported to have required extensive debridement of the perineum and subsequent skin grafting.⁷

Conclusion

Nicorandil is an important but poorly recognised cause of anal fissures and ulceration. Failure to recognise this drug as a cause can lead to considerable morbidity and unnecessary major surgery for patients. The required treatment is to stop the nicorandil, though this should always be done in consultation with an experienced cardiologist.

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