

Letters

NICORANDIL AS A CAUSE OF PERINEAL ULCERATION.

Editor,

We report a case of extensive perineal ulceration that healed spontaneously on discontinuation of nicorandil therapy, avoiding major perineal reconstructive surgery. We note a previous report of penile ulceration related to nicorandil therapy in this journal and wish to remind readers to consider nicorandil as a causative agent for any ulcerated non-healing chronic wound.¹

Case

An 82 year-old man presented with an 18 month history of painful perineal ulceration. He denied any other colorectal or gastrointestinal symptoms. His past medical history included myocardial infarction, atrial fibrillation and prostatic carcinoma. He received no radiotherapy to treat his prostatic carcinoma. He had been commenced on nicorandil 30mg twice daily 18 months previously following his myocardial infarction. Soon after this, he reports the gradual onset of painful perianal ulceration.

Biopsies performed by the referring specialty had excluded malignancy and inflammatory bowel disease. On initial review by Plastic Surgery he was found to have a deep 3x1cm area of ulceration adjacent to his anus, which was sloughy and had well circumscribed margins (Figure 1). Microbiological investigations were negative.



Fig 1. Ulcer at presentation.

Under the guidance of the patient's cardiologist, his nicorandil was discontinued and the dose of his Beta-Blocker was increased. On review at one month he was pain free and the ulcer was healing. At 5 months the defect had completely healed and he remained pain free.

Discussion

There are many causes of perineal ulceration for which malignancy and inflammatory bowel disease (Crohn's disease) account for the majority.^{2,3} Other causes include infective,

neoplastic, Extra-mammary Paget's disease, pharmacological and auto-immune.

Patients presenting to plastic surgeons with chronic perineal ulceration can have passed through several other specialties and have often undergone a plethora of haematological, microbiological, endoscopic and radiological gastrointestinal investigations prior to referral.² In addition they may have undergone several tissue biopsies.

Nicorandil is used as a third line agent in the treatment of angina and ischaemic heart disease.² Its pharmacological effects result in vascular smooth muscle relaxation dilating peripheral and coronary resistance arterioles, therefore increasing coronary blood flow.²

Nicorandil has been reported as a cause of mucosal ulceration in the gastrointestinal, gynaecological, surgical and urological literature.^{1,2,3,4,5} It has been associated with non-healing surgical wounds. Despite the link of nicorandil and painful perineal ulceration being reported in the literature, this patient passed through the care of a colorectal surgeon and the medical physicians prior to seeing the plastic surgeons. This would suggest that this link is not generally known about.

The onset of perianal ulceration after starting nicorandil can vary from several weeks to months, but healing on withdrawal of the drug is characteristic of nicorandil-induced ulceration. Some authors have suggested that the ulcerative effects of nicorandil may be dose dependent and patients on doses of 10mg daily are at risk of ulceration.

In summary

We report a case of extensive painful perineal ulceration that healed spontaneously on discontinuation of nicorandil therapy. Failure to recognise nicorandil as an aetiological factor in the development of perineal ulceration may lead to unnecessary surgical intervention.

The authors have no conflict of interest.

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REFERENCES

- 1 Kinney M, O'Rourke D, O'Kane H, Keane P, Nambirajan T. Nicorandil induced penile ulceration. *Ulster Med J.* 2010;**79**(3):123-4.
- 2 Cooke NS, Tolland JP, Dolan OM. Nicorandil-associated perianal ulceration: a case series of 10 patients. *Br J Dermatol.* 2006;**154**(1):199-200.
- 3 Katory M, Davies B, Kelty C, Arasaradnam R, Skinner P, Brown S, et al. Nicorandil and idiopathic anal ulceration. *Dis Colon Rectum.* 2005;**48**(7): 1442-6.
- 4 Chan SK, Harris MD, Baldwin PJ, Sterling JC. Vulvovaginal ulceration during prolonged treatment with nicorandil. *BJOG.* 2009;**116**(10):1403-5.
- 5 El-Dars LD, Bhagwanadas K, Hemmadi S, Hughes J. Nicorandil associated vulval and inguinal ulceration. *J Obstet Gynaecol.* 2009;**29**(7):674-5.

MASSIVE PULMONARY EMBOLUS PRESENTING WITH ABDOMINAL PAIN

Editor,

We present the case of a 20 year old man who presented to the emergency department of Craigavon Hospital with a one day history of abdominal pain and dyspnoea. He had been involved in a motorcycle accident three days previously and sustained a soft tissue injury to his left leg. Examination revealed lower abdominal tenderness and left calf swelling. Blood pressure was 140/53mmHg and oxygen saturations were 97% on room air. ECG showed sinus tachycardia (137 beats per minute) and 2mm upsloping ST segment elevation in leads V1-V4 (figure 1).



Fig 1.

Ten minutes after arrival, he had an asystolic arrest. Cardiopulmonary resuscitation was commenced, 10 units of intravenous reteplase were administered and he transferred to the cardiac catheterisation laboratory. Myocardial infarction was thought unlikely, thus we proceeded first to pulmonary angiography which showed a large filling defect in the main pulmonary artery extending into left and right branches consistent with a saddle embolism (figure 2). Catheter manipulation and direct intra-embolus injection of further reteplase achieved slight clot fragmentation into smaller sub-branches, but no significant return of pulmonary artery flow or systemic circulation. The resuscitation attempt was discontinued after 90 minutes. Autopsy confirmed a left leg

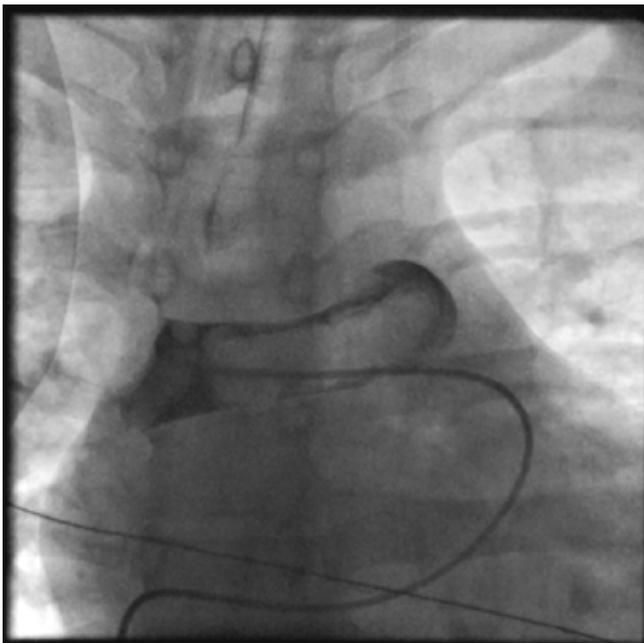


Fig 2.

deep venous thrombosis, a saddle-type pulmonary embolism and normal coronary arteries.

This case highlights the often atypical presentation of pulmonary embolism^{1,2}, the feasibility and value of early invasive pulmonary angiography even during cardiac arrest, but also the need for ongoing development of percutaneous techniques/devices for effective large-clot fragmentation or removal.

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REFERENCES

1. Henderson AF, Moran F, Banham SW. Pulmonary thromboembolism presenting as abdominal pain. *Br Med J (Clin Res Ed)*. 1984; **289(6449)**:902-3.
2. Potts DE, Sahn SA. Abdominal manifestations of pulmonary embolism. *JAMA*. 1976; **235(26)**:2835-7.

STREAMLINING THE USE OF IHC IN IDENTIFYING GERMLINE MISMATCH REPAIR MUTATIONS IN LYNCH SYNDROME.

Editor,

Colorectal cancer (CRC) is the second most common cause of cancer-related death¹. Inherited genetic factors are significant in <30% of cases. In ~5% of all cases², CRC is associated with a highly penetrant dominant or recessive inherited syndrome. The most common of these is Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC), an autosomal dominant cancer susceptibility syndrome caused by a germline mutation in one of the DNA mismatch repair (MMR) genes, namely MLH1, MSH2, MSH6 or PMS2. Affected individuals have a predisposition to developing early onset CRC and a range of other cancers, particularly endometrial in females. The associated lifetime cancer risk is 75%². Early diagnosis enables at risk family members to be enrolled in appropriate cancer surveillance programmes, thus reducing mortality and morbidity. Additionally, recent studies have indicated a role for aspirin in reducing Lynch syndrome tumours³.

MMR defect leads to instability in microsatellites of tumour DNA. This feature can be found in >90% of colon cancers associated with Lynch syndrome, compared to ~ 15% of cases of sporadic CRC². Using immunohistochemistry (IHC), tumour analysis with antibodies against the four MMR proteins demonstrates loss of protein expression of the causative gene. This investigation thereby provides early, valuable identification of possible HNPCC-related tumours. It furthermore directs germline mutation screening to the gene involved, significantly reducing the time and cost involved in

searching for a causative mutation and prioritising families in which this limited resource should be applied. When individuals are identified with a germline MMR mutation, there are implications for long term screening requirements and possible prophylactic gynaecological surgery to reduce cancer risk⁴. Germline mutation identification also allows predictive testing for at risk family members.

Currently the Amsterdam criteria II and revised Bethesda guidelines are used to identify families with potential Lynch syndrome for further investigation (Box 1). MMR IHC provides key information in this assessment. Delay in the time taken to obtain IHC results negatively impacts upon the overall time to obtain germline mutation screening results. While awaiting germline mutation screening, individuals and their relatives may either not access appropriate screening or may undergo serial, unnecessary screening with associated risks and anxieties.

The authors performed a study to assess current regional practice in utilising MMR IHC⁵. 32 patients were identified with abnormal MMR IHC. Of these, six fulfilled Amsterdam criteria II and 26 fulfilled revised Bethesda criteria. 23 had CRC at an average age of 48 years (range 32-76). 11 had endometrial cancer at an average age of 56 years (range 36-67). The median wait for MMR IHC result was 69 days from time of request (range 1-588 days). Causes of delay included time required to locate appropriate pathology records, request pathology tissue for testing (from a range of pathology laboratories) and perform and interpret the assay. In 26 of 32 cases, IHC was requested by the clinical genetics team at the time of first genetics clinic appointment.

We would encourage our surgery and pathology colleagues to consider the diagnosis of Lynch syndrome and adopt the practice of requesting MMR IHC (where cases fulfill revised Bethesda criteria) at the time of surgery or prior to referral to clinical genetics, in order to streamline the investigation of possible Lynch syndrome and expedite germline mutation identification in such families.

The authors have no conflict of interest.

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REFERENCE

1. Cancerstats: Mortality (UK): Common Cancers. Deaths from common cancers. UK mortality statistics. London: Cancer Research UK. 2009 [Updated 2011 Nov 13]. Available from: <http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths>. Last accessed March 2012.
2. Vasen HI, Moslein G, Alonso A, Bernstein I, Bertario L. et al. Guidelines

Box 1 Amsterdam criteria II and revised Bethesda guidelines **

Amsterdam criteria II

There should be at least three relatives with colorectal cancer (CRC) or with a Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.

- one relative should be a first-degree relative of the other two,
- at least two successive generations should be affected,
- at least one tumour should be diagnosed before the age of 50 years,
- familial adenomatous polyposis (FAP) should be excluded,
- tumours should be verified by histopathological examination.

Revised Bethesda guidelines

1. CRC diagnosed in a patient aged <50 years.
2. Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours*, regardless of age.
3. CRC with MSI-H phenotype diagnosed in a patient aged <60 years.
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age <50 years.
5. Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumour, regardless of age.

* Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

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for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet*. 2007; **44**(6); 353-62.

3. Burn J, Mathers JC, Gerdes AM, Bisgaard M, Evans G. et al. Cancer occurrence during follow-up of the CAPP2 study-aspirin use for up to four years significantly reduces Lynch syndrome cancers for up to several years after completion of therapy. *Hereditary Cancer Clin Pract*. 2010; **8** (Suppl 1):05. Available from: <http://www.hccpjournals.com/content/8/51/05>. Last accessed March 2012.
4. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB. Prophylactic Surgery to Reduce the Risk of Gynaecologic Cancers in the Lynch Syndrome *New Engl J Med*. 2006; **354**(3):261-9.
5. Rea G, Magee A, Loughrey M. Optimising the application of IHC in identifying germline MMR mutations in HNPCC. *Ulster Med J*. 2011; **80** (3):169- 70.