Lesson of the Week

Haematuria in patients with haemostatic defects

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Haematuria is a common feature of haemophilia and von Willebrand's disease, as many as 90% of severely affected patients having at least one episode in their lifetime.¹ The clinical course is well documented, usually arising and resolving spontaneously even before the advent of specific treatment.² It has been shown not to be associated with progressive loss of renal function and is generally believed to be benign.³ We describe a case of persistent haematuria over one year due to renal carcinoma in a patient with von Willebrand's disease; the carcinoma remained undetected despite routine pyelography and renography and was found by ultrasound scanning. To our knowledge this has not been described in von Willebrand's disease or the haemophilias.

Case report

A 31 year old man with known severe von Willebrand's disease (bleeding time 28 minutes; ristocetin cofactor 38% of normal) was admitted with spontaneous gross haematuria and right sided renal colic. He was otherwise well with no other urinary symptoms, and no abnormal findings were apparent on physical examination. Results of urine culture were negative and serum urate, calcium, phosphate, urea, creatinine, and electrolyte concentrations were normal. Full blood count was normal, with a haemoglobin concentration of 15.5 g/dl and normal white cell count. An isotope renogram showed no evidence of obstruction. He was treated with cryoprecipitate, fluids, and analgesics and the haematuria settled after one week.

Two months later a similar episode occurred and was complicated by bladder outflow obstruction secondary to clot. Results of urine bacteriology and of biochemical investigations were again normal. Haemoglobin concentration had fallen to 12.7 g/dl, blood film showed early iron deficient changes, and white cell count was normal. An intravenous urogram showed a normal kidney and collecting system on the left, while on the right a large dense nephrogram was apparent with delayed excretion of dye (fig 1). The right ureter was not visualised at any stage in the examination, and the dense nephrogram was still present on the two hour film. These appearances were compatible with obstruction, probably secondary to blood clot in the ureter. Again the haematuria settled with cryoprecipitate and fluids. A further admission was required one month later for haematuria and renal colic. The patient denied any other symptoms and his general health was otherwise good. There were no abnormal findings on physical examination. Biochemical and bacteriological investigations again showed no abnormalities, haemoglobin was 13.2 g/dl, and blood film and white cell count were normal. An isotope renogram showed reduced function and obstruction on the right, and the differential function was 80% (left) to 20% (right). Intravenous urography again showed delayed excretion and a large, dense

Haematuria in patients with haemostatic defects may not always be due to the primary disease

nephrogram on the right, which persisted up to the two hour film. The ureter was not visualised at any stage. After treatment with cryoprecipitate the haematuria settled.

Over the next three months he continued to have episodes of haematuria despite prophylactic treatment with cryoprecipitate two or three times weekly as an outpatient. Isotope renography was repeated to assess renal

FIG 1—Intravenous urogram showing dense nephrogram on right (10 minute film).

function and obstruction and showed good perfusion to the upper pole of the right kidney with normal excretion; differential function was within normal limits. Two months later the haematuria and renal colic recurred: there were no other symptoms, and results of physical examination and bacteriological and biochemical investigations were once again normal. Haemoglobin concentration had fallen to 11.8 g/dl, with an iron deficient film and normal white cell count. Cystoscopy and right sided retrograde pyelography showed no abnormality, apart from slight blunting of the calices, which was considered to be due to the infusion pressure of the dye. We therefore thought that this was a coagulation rather than a structural renal problem and prophylactic treatment with cryoprecipitate was continued. After a further episode of haematuria treatment was augmented with the anti-

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fibrinolytic agent tranexamic acid.¹ Treatment with intermittent cryoprecipitate and tranexamic acid was continued for five months, during which several minor episodes of haematuria occurred but no episodes of obstruction.

One year after the first episode he was still having problems with haematuria and colic, but otherwise he remained well and physical examination showed nothing abnormal. We decided that further investigations were again warranted. Biochemical and bacteriological findings remained normal, haemoglobin concentration was 16.6 g/dl, and white cell count was normal. Isotope renography disclosed a large, irregular right kidney. Ultrasound and computed tomography showed that the right kidney had been replaced by an irregular mass (fig 2); there was no evidence of para-aortic lymphadenopathy. Right sided radical nephrectomy was performed uneventfully under cryoprecipitate cover, and at the time of operation there was no evidence of extrarenal spread. The lesion was a large clear cell carcinoma (65×65×50 mm) affecting the renal pelvis. Renal vein and ureter were clear of tumour. Radiography of the chest and a bone scan showed no evidence of metastases. He made a good postoperative recovery and remained well.

FIG 2—Computed tomogram of upper abdomen after contrast enhancement showing large right sided mass replacing kidney.

Comment

This case highlights the difficulties of investigating haematuria in patients with hereditary coagulation disorders. Bleeding from the urinary tract is the second most common manifestation of haemophilia.¹ In addition, one fifth of asymptomatic patients have subclinical haematuria.⁴ It is thought to follow a benign course, though problems may arise secondary to clot causing obstruction.¹ Paradoxically clot may occur in the urinary tract of these patients even without treatment due to naturally occurring thromboplastins in the urine, and treatment with both cryoprecipitate and anti-fibrinolytic agents may result in further clot which can produce obstruction and renal failure.¹ Routine use of fibrinolytic inhibitors is therefore not recommended. They may, however, be used in patients in whom bleeding continues despite adequate haemostasis and in whom structural problems have been excluded,¹ but the clinician must weigh the risks of treatment against the risk of further bleeding, including the psychological and social problems of recurrent bleeds and hospital admissions. In a series of 57 patients, including 27 who were followed up over 11 years, very few structural problems were found and often these did not persist.³

In view of these studies there appears to be little justification for extensive investigation of every episode of haematuria in patients with coagulation disorders, especially with the amount of radiation exposure required for intravenous urography. Since obstruction is the main complication, isotope renography with its low radiation exposure is useful for assessing obstruction and function. Intravenous urography is, however, required to exclude an organic lesion, but obstruction by clot may prevent adequate excretion of the dye with consequent poor visualisation of the collecting system.

Arteriography is generally contraindicated in these patients owing to the hazard of extensive bleeding. In classic haemophilia there is a good correlation between clinical symptoms and laboratory assessment of disease severity, allowing accurate prediction of clinical response and the amount of treatment required; the treatment of von Willebrand's disease, however, remains empirical. This is due to the great variation in individual response to treatment and the fact that bleeding from mucosa and skin may not be controlled, even if very high factor VIII concentrations are obtained.⁵ Consequently any surgical procedure may be hazardous in these patients, as the amount of treatment required and the response to it cannot accurately be forecast.

Despite frequent clinical examination and investigation our patient remained undiagnosed until ultrasound and computed tomography were performed. In retrospect enlargement of the right kidney might have suggested a neoplasm despite the young age of the patient. Nevertheless, renal enlargement due to obstruction by blood clot is documented in haemophilia.¹ In this case ultrasound was not performed earlier as we were reassured by the intravenous urogram and retrograde pyelogram that no structural lesion was present; and the problem was in keeping with previous experience of spontaneous haematuria in patients with coagulation disorders.³

The investigation of haematuria in these patients has centred on intravenous urography and isotope renography.¹ We suggest that in addition ultrasound should be used in their routine investigation. Clinicians should be alert to the possibility that recurrent haematuria in this particular group is not always related to their coagulopathy and may herald a neoplasm, even when renography and urography show nothing abnormal.

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An otherwise active and healthy woman of 64 who had a hysterectomy for irregular bleeding 10 years ago (non-malignant) continues to have, almost nightly, hot flushes that waken her and prevent her returning to sleep. What might be the cause and how should she be treated?

This patient presumably had bilateral oophorectomy at the time of her hysterectomy. Flushes are the commonest symptom of the menopause, occurring in up to 85% of women,¹ and although their maximum incidence is in the year after the periods stop, a few women have flushes for up to ten years. In one study a questionnaire was sent to women aged 45-54, and 29% of those whose menopause had occurred more than nine years previously said that they had experienced a hot flush within the past year.² The standard treatment is oestrogen, which relieves vasomotor symptoms in over 90% of patients—though I am uncertain how effective it would be ten years after the menopause. Ethinyl oestradiol may be given without an added progestogen to a woman who has had a hysterectomy. According to a recent report subcutaneous implants of oestradiol and testosterone are particularly successful in relieving climacteric symptoms.³ When oestrogen is contraindicated, progestogen treatment with medroxyprogesterone acetate may help.¹ An alternative is clonidine, 25-75 µg twice daily, though its effectiveness has been questioned. Other causes of flushing—for instance, carcinoid syndrome—are rare and usually produce other symptoms.—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

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