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Successful management of severe refractory haemorrhagic cystitis secondary to cyclophosphamide and BK virus with cystotomy and alum infusion☆

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ABSTRACT

A 36-year-old male patient is referred for urology review for haematuria following cyclophosphamide and mesna administration for allogeneic stem cell transplant for treatment of acute lymphoblastic leukaemia. Severe haematuria continued despite multiple interventions including continuous bladder irrigation and cystoscopic fulguration, with formation of consolidated clot in the bladder. A successful cystotomy for removal of clot and initiation of alum was performed, leading to resolution of haematuria.

Introduction

Although haemorrhagic cystitis is not uncommon following cyclophosphamide chemotherapy, treatment of this entity following exhaustion of conservative measures can be challenging. This report describes a case of successful recovery from severe refractory haemorrhagic cystitis caused by cyclophosphamide and BK virus, despite multiple surgeries including cystotomy for clot evacuation and diathermy. This case demonstrates that cystotomy may be considered as an alternative approach in management of haemorrhagic cystitis in patients where adequate control is not achievable with cystoscopic fulguration prior to consideration of more radical approaches.

Case history

A 36-year-old otherwise healthy man was referred to urology for management of haemorrhagic cystitis following a planned admission allogeneic stem cell transplant for acute lymphoblastic leukaemia. The patient was given 2 days of cyclophosphamide and mesna 14 days prior in conjunction with total body irradiation as part of myeloablative protocol for the transplant. At time of initial assessment by urology, the patient had new onset haematuria, associated with pancytopenia and a platelet count of 22 $\times$ 10^9/L. A CT intravenous pyelogram conducted at this time revealed bladder wall thickening and fat stranding suggestive of cystitis, with no clot burden.

The haematuria was monitored for several days with trial of rehydration. A 2-way IDC was initially inserted for fluid balance monitoring following an episode of febrile neutropenia, and was promptly changed to 3-way IDC due to worsening of haematuria, with clots. A severe oral mucositis also developed at this time, requiring intubation. BK virus screening in blood returned positive at this time.

Despite continuous bladder irrigation and frequent manual washouts, the patient developed significant clot burden on ultrasound and recurrent blockages of his in-dwelling catheter, with ongoing transfusion requirements. This issue was compounded by the initiation of defibrotide for treatment of veno-occlusive disease. The patient was taken to theatre for clot evacuation and diathermy. Although initially successful, haematuria recurred in the following week, and repeat cystoscopy was performed revealing rapid ongoing clotting despite copious washout and clot evacuation.

A progress CT scan revealed large amounts of residual clot, with associated bladder wall thickening and stranding (Fig. 1), and a repeat cystoscopy was conducted 2 days later. Extensive clots were found in the bladder, and due to ongoing significant bleeding a decision was made to conduct a cystotomy, delivering a 20 $\times$ 10cm clot (Fig. 2), and to commence alum irrigation.

Haematuria gradually improved in the following month, and completely resolved with one further cystoscopy for bladder washout 3

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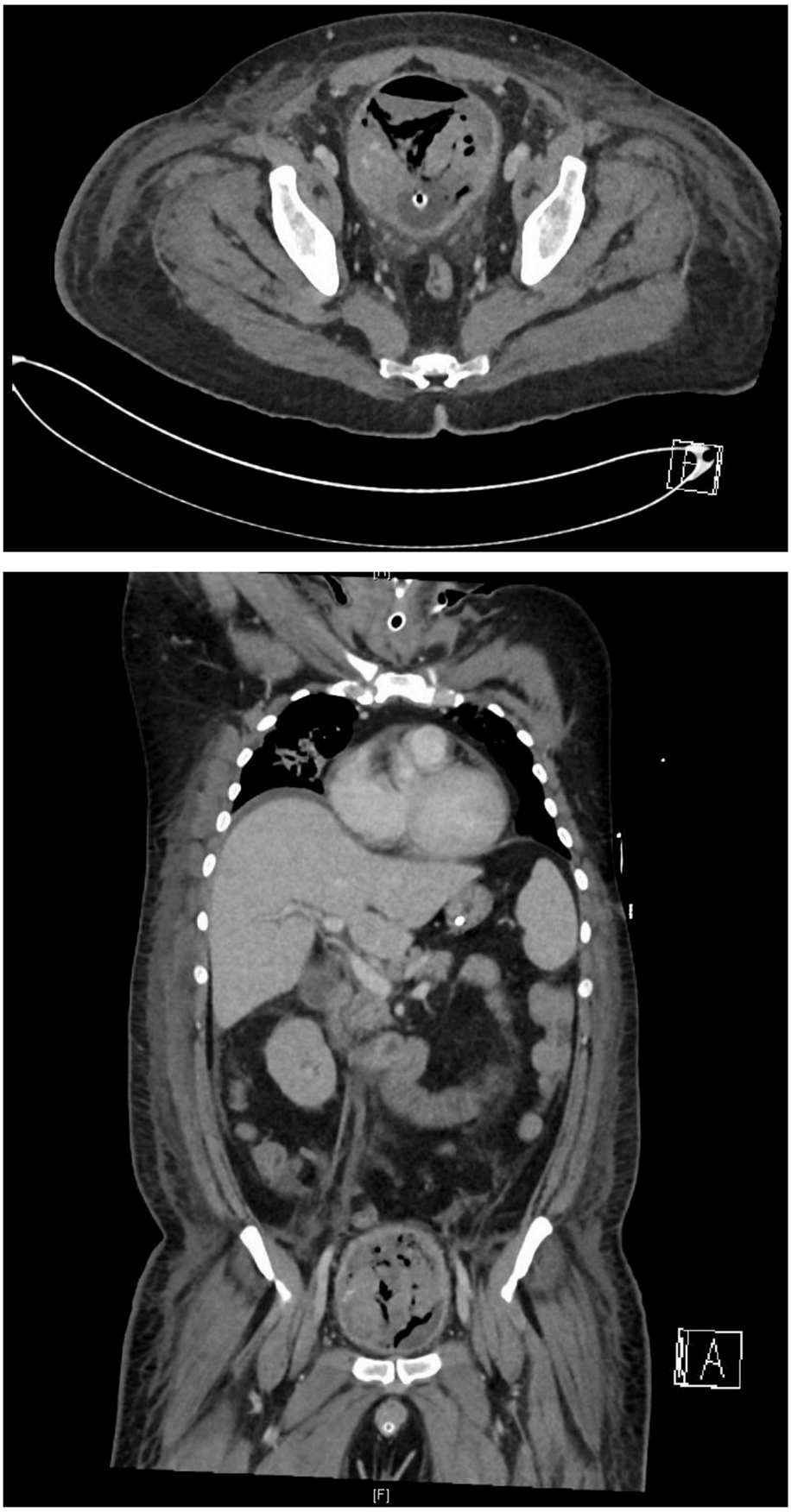

Fig. 1. CT scan conducted 2 days prior to third cystoscopy, showing large volume intravesical blood clots, with features of cystitis. (a) Axial view (b) Coronal view.

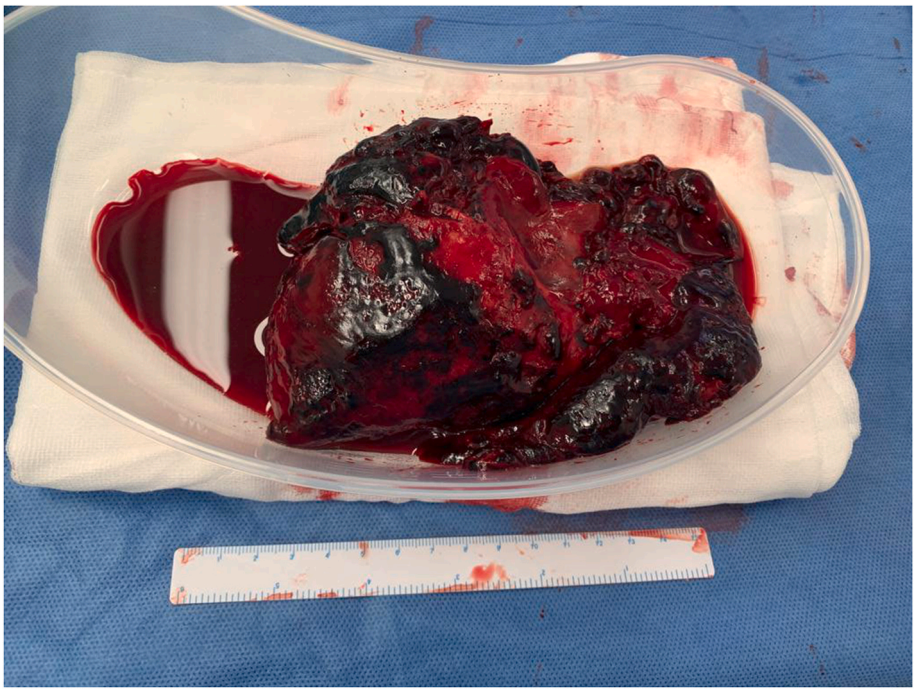

Fig. 2. Clinical image of blood clot removed during cystotomy.

weeks later. The patient subsequently passed a trial without catheter the week following. The patient's urine remained clear at 3-month follow-up, and irritative voiding symptoms following catheter removal responded well to oxybutynin and mirabegron.

Discussion

Haemorrhagic cystitis occurs in approximately 16% of allogeneic hematopoietic cell transplantation, in which 56% of patients developed macroscopic haematuria with clots.[1] Cyclophosphamide increases the risk of developing haemorrhagic cystitis, due to production of the urinary metabolite acrolein, which induces urothelial cell necrosis through overactivation of the DNA repair enzyme polyadenosine diphosphate-ribose polymerase (PARP).[2] Mesna acts in the urine to bind and neutralise the effect of acrolein on urothelium. Hence, it is commonly used in conjunction in chemotherapy protocols with cyclophosphamide as a prophylactic measure against haemorrhagic cystitis, although its efficacy is disputed.[3]

It is difficult to manage severe haemorrhagic cystitis due to the lack of consensus on its optimal treatment following failure of saline continuous bladder irrigation. Suggested therapies in the literature are similar whether thought to be caused primarily due to BK viruria or acrolein. Mild haemorrhagic cystitis can be managed with hydration or continuous bladder irrigation. Severe cases may require consideration of more invasive surgical procedures such as nephrostomy urinary diversion or cystectomy which, although effective, is associated with high morbidity and mortality, and therefore conducted only as the last option.[4]

Several agents have shown varying efficacy in treatment of haemorrhagic cystitis; intravesical therapies include alum infusion, chondroitin, prostaglandin, formalin and sodium hyaluronate while systemic therapies include hyperbaric oxygen and oestrogen.[3,4] Although other intravesical instillations may also assist in treatment in this case, intravesical alum was used due to relatively established evidence in prior studies, availability in pharmacy and its relatively few adverse effects.

It is recommended to precede intravesical therapy by removal of residual clots from the bladder.[4] This is usually conducted through manual bladder washout, with or without addition of cystoscopic fulguration under general anaesthesia. Given multiple attempts at this without success in this case, we adopted an open approach to clot evacuation. Although open cystotomy has been used for other indications such as removal of stones or foreign objects, removal of clots with this method has not been reported in the literature.

In this case, nephrostomies were not inserted due to the requirement for clot removal, and marked improvement in bleeding following operative clot clearance and intravesical alum infusion. Our unique approach proved effective in managing the patient's haemorrhage, preventing the need to consider more radical procedures such as cystectomy and formation of ileal conduit, which would carry significantly higher risks to the patient. To our knowledge we report the first successful case of managing haemorrhagic cystitis with open cystotomy.

Conclusion

In the context of significant clots burden refractory to repeated endoscopic approach, swift clinical judgement and precise surgical decision should be made, such as in this case, conversion to open approach to stop bleeding and evacuate clot. This can lead to better patient outcomes and earlier resolution of symptoms, with reduced number of operations and general anaesthetics in high-risk patients.

Declaration of competing interest

None.

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