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Refractory bladder haemorrhage managed with cystoscopic diathermy in a patient with Ataxia-Telangiectasia and intercurrent BK polyomavirus infection

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ABSTRACT

Ataxia telangiectasia (A-T) is a rare neurodegenerative immunodeficiency syndrome, characterised eponymously by progressive cerebellar ataxia and telangiectatic vessels, most often cutaneous. A-T displays autosomal recessive inheritance, is characterised by defective DNA repair due to mutations within the ATM gene on chromosome 11 [1]; and a lack of native ATM protein gives rise to the aforementioned hallmarks of the disease. With A-T comes a predisposition to haematological malignancy and humoral immunodeficiency, and as such these patients often suffer truncated lifespans [1,2]. Urological manifestations are rare, and intravesical involvement comprising bladder telangiectasia has only been described in a handful of cases, all of which have previously been treated with cyclophosphamide for malignancies, a known instigator of bladder haemorrhage [3–5]. Similarly, BK polyomavirus is a known precipitant of nephropathy and haemorrhagic cystitis in actively immunosuppressed renal transplant patients, though has not been established as such in genetically immunodeficient patients with native urological tissue [6]. Here we present, to our knowledge, the first case of refractory haemorrhagic cystitis in an A-T patient with intercurrent BK polyoma virus infection, who had previously been treated with cyclophosphamide for leukaemia, and propose that recurrent cystoscopic diathermy is a robust and relatively conservative surgical option to treat haemorrhagic cystitis secondary to bladder wall telangiectasia.

1. Case report

Here we report the case of a 14-year-old female with ataxia-telangiectasia (A-T), and concomitant T-cell acute lymphoblastic leukaemia, previously treated with cyclophosphamide in 2016. She initially presented to a peripheral hospital in acute urinary retention, with a 3-month history of macroscopic haematuria and intermittent passage of clots. Over a 17-h period of observation, the patient passed multiple large blood clots upon forceful voiding and did not require bladder catheterisation nor irrigation. Serial post-void bladder scans revealed negligible volumes, demonstrating resolution of her retention following the passage of clots. The patient's haemoglobin at presentation was stable at 96g/L in comparison to 100g/L 2 months prior, (4 weeks after the onset of macroscopic haematuria). However, a marked drop in haemoglobin became apparent upon review of multiple measurements 6 months prior, demonstrated a baseline ranging from 122 to 138g/L. Platelets were stable at 488 × 10^9/L at presentation, and were similarly robust over the preceding months. Urine MCS grew *Klebsiella pneumoniae* x10^8, which was sensitive and subsequently treated with oral

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amoxicillin/clavulanate. A renal tract US performed only weeks prior to her presentation to investigate her haematuria demonstrated normal anatomy with no overt structural cause identified. The patient was diagnosed with haemorrhagic cystitis secondary to *Klebsiella* UTI and referred onto our specialist urology service given her complex medical history, duration of symptoms and seemingly refractory nature of her haematuria.

Over the ensuing 6 weeks, the patient experienced persistent macroscopic haematuria despite adequate treatment of her UTI, and was subsequently booked for exploratory cystoscopy. Whilst awaiting cystoscopy, the patient re-presented with an acute episode of urinary tract haemorrhage. She was incontinent of urine with frank haematuria, continually passing large clots, and was pale and lethargic. Her haemoglobin was found to be 38g/L, whilst platelets remained robust at 472 × 10^9/L, renal function and coagulation profiles were preserved. Urine MCS again demonstrated *Klebsiella pneumoniae* x10^8. Remarkably, the patient remained haemodynamically stable, and was transfused with packed red cells and given tranexamic acid prior to proceeding semi-urgently to cystoscopy. Intraoperative findings included a large ~60ml clot and frank blood-stained urine within the bladder, with multifocal active bleeding from a conglomerate of abnormal vessels within the bladder wall. No attempt at diathermy to these vessels was made due to a constantly obscured view from ongoing bleeding, and so a 3-way catheter was inserted to facilitate bladder irrigation in the interim. Notably, the patient's urine was positive for BK polyomavirus at this time (with no prior urinary polyomavirus testing performed).

Repeat cystoscopy 2 weeks later revealed widespread bladder telangiectasia and diffuse ooze from these vessels. Diathermy to all actively bleeding telangiectasia was performed over a 2-h intraoperative period, with no active bleeding at completion of the procedure. Post-operative haemoglobin was 79g/L, and the patient was subsequently transfused with 1 unit of packed red cells, bringing this parameter up to 93g/L the following day.

The patient has since undergone 5 further planned cystoscopies and diathermy to telangiectatic vessels, initially at 1–2 week intervals guided clinically by progressive haematuria, until a 10-week reprieve was reached. At each subsequent procedure, multiple large clots were again encountered within the bladder, as well as widespread bleeding from multiple telangiectasias within the mucosal wall, despite a visible response to previous treatment. Interestingly, the patient's haemoglobin has remained stable within the range of 98–122g/L without requiring red cell transfusions whilst having planned procedures at a maximum of 2-week intervals. Where her third repeat procedure was stretched to a 3-week interval, she presented to the emergency department with a haemoglobin of 61g/L and proceeded to cystoscopy that same day following red cell transfusion. She continued to experience macroscopic haematuria between each procedure, which progressively worsened throughout the 1-2-week timeframe, and continued on oral tranexamic acid throughout these intervals. At her penultimate cystoscopy, the major finding was marked sloughy tissue throughout the bladder, and only sparse foci of bleeding vessels which were again diathermied, thus the timing of repeat cystoscopy was left to be determined by the patient's clinical course. She underwent her 5th and final cystoscopy to date 10 weeks later, due to a febrile illness presumed to be urosepsis given the intravesical slough noted previously, rather than due to decompensated haematuria. Notably, there were no bleeding vessels present, despite their persistent prominent appearance, and the bladder mucosa appeared much healthier. The patient's humoral immunodeficiency renders her dependent on monthly intravenous immunoglobulin (IVIg), which has been continued throughout her urological treatment, and she remains on daily oral 6-mercaptopurine as treatment-with palliative intent-for T-ALL. All diagnosed UTI's throughout this 6-month period were treated in a timely manner with an appropriate antibiotic agent. She has remained on prophylactic bactrim since her 4th cystoscopy.

2. Discussion

Telangiectasia constitutes the insignia of A-T, and most commonly occurs as oculocutaneous lesions and sun-exposed cutaneous lesions, particularly of the head and neck [2]. Far less common is telangiectasia confined to organs, though small numbers of case reports do describe diseased vessels involving the intestinal mucosa and cerebral vasculature [3,7]. Telangiectasia of the bladder mucosa is exceedingly rare, only being reported a handful of times since first being described in 2008 [8]. Equally rare within the spectrum of symptomatology in A-T is bleeding from telangiectatic lesions such that haemodynamic stability- and survival-is threatened, with the exception of bladder wall telangiectasia [8]. Indeed, the majority of studies which report bladder telangiectasia in the setting of A-T describe 'severe haemorrhagic cystitis' [3], 'massive haematuria' [9], and 'life-threatening haematuria' [8], the mainstay of this presentation.

Interestingly, all patients reported to have bladder telangiectasia in association with A-T have also been treated with cyclophosphamide for concomitant haematological malignancies at some point prior to presenting with haematuria [3,8,9], though not all A-T patients who have had cyclophosphamide go on to develop haemorrhagic cystitis. What remains to be elucidated relates to cause or effect. Haemorrhagic cystitis is a well-documented adverse reaction to cyclophosphamide, due to exposure of the bladder mucosa to the corrosive metabolite acrolein via renal excretion [10]. It has been proposed that defective cell cycle arrest conferred from mutations in the ATM gene renders the bladders of A-T patients unable to neovascularise in response to recurrent erosion in the presence of cyclophosphamide. This infers that bladder telangiectasiae form within the mucosa in response to cellular damage [8]. Alternatively, it may be that telangiectasiae are pre-existing and present within the deeper mucosal layers of the bladder, which then only become clinically apparent once the urothelium is under attack. This may be akin to the seemingly dormant nature of telangiectasia in cutaneous & cerebral and distributions which have simply not been exposed to caustic environments. Perhaps we don't see severe haemorrhaging from these vessels because they simply have not encountered a toxic/infectious attack. Whilst cyclophosphamide alone is widely accepted to be a cause for haemorrhagic cystitis, here we propose a 'perfect storm' of haemorrhagic hits that subsequently predispose A-T sufferers to life-threatening haemorrhage. To our knowledge, there exists no histological data comparing haemorrhaged intravesical tissue of an individual whom has received cyclophosphamide with A-T to that without A-T, and certainly not to an A-T sufferer with previous cyclophosphamide exposure and superimposed BKV infection. Though this data would likely highlight the

extent to which A-T alone (and additionally superimposed infection) contributes to haemorrhagic cystitis over cyclophosphamide alone, it would require at least partial cystectomy, which would be a grossly unfavourable outcome for the patient in comparison to less aggressive measures. Nonetheless, we propose that the nature and proven histology of telangiectatic vessels place A-T patients with intravesical involvement at an increased risk of life-threatening haemorrhage, compounded by the fact that they have invariably had cyclophosphamide treatment, and that concomitant infection with organisms known to be associated with haemorrhagic cystitis is likely to increase this risk immensely.

BK polyomavirus is similarly a well-established culprit of haemorrhagic cystitis in bone marrow and renal transplant patients [3], though is thought to be quite a rare cause of such in other immunodeficiency disorders involving native tissue [11]. Although the exact mechanism of activation remains unclear, the BK virus transitions from innocuous colonisation within the urothelium throughout the general population, to uncontrolled replication in an immunocompromised host, such that the sheer volume of the viral load within the mucosa causes severe cystitis and haemorrhage [12]. To our knowledge, this is the first report of active BK infection in the setting of urinary tract haemorrhage in an A-T patient. Interestingly, the patient's urinary (excretory) BK viral load increased during her period of remission post her 5th cystoscopy, which may reflect intravesical scarring such that the same virulence factors can no longer infiltrate the mucosa to cause haemorrhage. Christmann et al. [3] report a case of haemorrhagic cystitis in an A-T patient, in the context of previous cyclophosphamide and concurrent JC polyomavirus infection, although neither the extent of anaemia or management techniques to control the haematuria were addressed. Interestingly, a systematic review of therapeutic options for BK-associated haemorrhagic cystitis demonstrated low-quality evidence for all current modalities, including prophylactic quinolones, leflunomide, cidofovir fibrin glue, hyperbaric oxygen therapy and intravesical alum, and there remains no unifying therapeutic option to treat polyoma associated haemorrhagic cystitis or to eradicate the infection [6]. Despite the lack of effective antiviral treatments, the presence of BK or JC viruses within the urothelium of a potentially already compromised mucosa-particularly in the setting of cyclophosphamide exposure-must certainly predispose A-T patients to an even greater risk of severe and life-threatening haematuria, and firstly must be tested for at presentations of haemorrhagic cystitis in this cohort, and secondly must factor into surgical decision making.

Notably, the only difference in management between the timeframe where fortnightly cystodiathermy was required and the 10-week reprieve was the presence of an IDC for 2 weeks post-penultimate cystoscopy. From the commencement of our treatment, the bladder had decreased significantly in size to have only 100ml capacity at the penultimate procedure, and leaving the IDC in likely allowed the bladder to remain decompressed and likely prevented these fragile vessels from suffering the forces of distension and re-bleeding.

A handful of variable management regimes have been described in relation to bladder haemorrhage in the setting of A-T, and no single regime has declared itself the gold standard, as each seems to be tailored to the individual patient with regard to clinical stability, severity of bleeding, chronicity of bleeding, comorbid prognoses, and the experience of the attending clinician. Treatment options for bladder telangiectasia range from simply 3-way bladder irrigation in conjunction with red cell transfusions to more radical measures such as partial cystectomy [9,13]. We have been managing our A-T patient's bladder telangiectasia for 1 year, and have utilised cystoscopic diathermy as our mainstay of treatment, firstly as it served as a relatively fast, definitive and conservative surgical method to allay life-threatening intravesical bleeding and stabilise our severely anaemic patient, and secondly because we feel that the clinical trajectory for this patient remains unclear. Our goal was to employ the most conservative method to allay bleeding from the outset, and recurrent cystodiathermy became a reliably effective method to treat progressive haematuria in a manner that resolved bleeding quickly, minimised inpatient stays (as all planned cystoscopies were day cases), and prevented undue trauma relating to awake alternate treatment options. Continuous bladder irrigation with red cell transfusion and intravesical alum remain the mainstays of medical treatment for haemorrhagic cystitis, and though considered, were felt to be inappropriate due to the burden of extended hospital stays, the relatively high chance of failure-approximately 40% [14]- and the subsequent life-threatening risk that ineffectual treatment posed to this patient. Our institution has previously utilised intravesical alum unsuccessfully, where the patient suffered intractable bladder spasm, iatrogenic trauma, and ultimately required a total cystectomy for refractory haemorrhage, which understandably affected our treatment decision.

We feel our approach has benefited the patient and her family in a multitude of ways that outweigh the downsides, of which include frequent hospital visits and general anaesthetics, an increased risk of infection with recurrent instrumentation, a marked reduction in bladder capacity. Thus far, we have thankfully avoided committing the patient to multiple major operations, as would be inevitable with more invasive surgical options. More permanent options, such as diverting ureterostomy, cystectomy and bladder artery embolization, bring with them potentially greater morbidity and significantly greater logistical challenges in the setting of a child with progressive functional and neurodegenerative decline, and must be considered carefully in the context of not only quality of life but also with consideration of the patient's life expectancy. Our approach is, in essence, a palliative approach in that it has allowed the patient and her family to maintain quality of life by avoiding major operations and extended hospital stays, and similarly has cumulatively treated her haematuria such that unpredictable and frequent hospital trips for symptomatic bleeding have abated, as has her families anxiety about recurrent life-threatening bleeds. The patient continues to enjoy a reasonably high quality of life in terms of cognitive function and mobility, and though her prognosis remains unclear, we expect to see her reach young adulthood, as is the average life expectancy for a patient with A-T.

3. Conclusion

We propose that the cumulative effect of recurrent cystodiathermy and in-dwelling catheter decompression prevents re-distension of friable telangiectatic vessels, and in combination with timely and appropriate antibiotic treatment and ongoing prophylaxis for

urinary tract infections, has allowed our patient apparent remission over the past 6 months from her recurrent urinary tract haemorrhaging. At current, she suffers only intermittent microscopic haematuria, without haemodynamic compromise or an associated drop in haemoglobin. The resultant reduction in bladder capacity likely represents a degree of scarring and contracture which negates recurrent bleeding from telangiectatic vessels.

The combination of previous cyclophosphamide, active BK polyomavirus infection and intercurrent *Klebsiella pneumoniae* infection may indeed have created the perfect storm in terms of precipitating catastrophic urinary tract bleeding in this patient, in terms of adding insult to an already compromised mucosa. Prophylactic measures may be prudent in this cohort of patients in an attempt to avoid life-threatening haemorrhage, including consideration of alternative chemotherapeutic agents to cyclophosphamide (ensuring uroprotective measures if it must be used), diligent UTI surveillance with timely diagnosis and treatment and consideration of prophylaxis, and early urinary polyoma virus testing which may aid in prognostication.

Further research is needed to characterise the native A-T bladder, to determine whether certain subpopulations indeed have long-standing bladder telangiectasia, which only haemorrhage in superimposed hostile conditions, or whether cumulative toxic/infective insult induces these telangiectatic vessels to form and subsequently bleed. A-T patients would also stand to benefit from further developments in polyomavirus treatment and potential prophylactic options.

We would advocate for the most conservative surgical management option possible to facilitate resolution of haemorrhagic cystitis, given the comorbid complexities faced b A-T patients, and propose that recurrent cystodiathermy is an effective, safe method by which to achieve this, whilst maintaining the patients' quality of life.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Declaration of competing interest

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