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Presentation of case: Bladder cancer in an 18 year old female patient

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ABSTRACT

INTRODUCTION: Bladder cancers are not very common in the young population below 20 years of age, especially in those who have not been exposed to chemotherapy, bladder augmentation surgery and other known risk factors. By highlighting this case we hope to raise awareness in the medical community, that the symptom of visible haematuria can potentially be due to a bladder malignancy and therefore this should be thoroughly investigated.

PRESENTATION OF CASE: An 18-year-old female presented with intermittent macroscopic haematuria and non-specific abdominal pain. Physical examination and routine blood tests were normal. An ultrasound scan initially showed a bladder wall lesion, which a flexible cystoscopy confirmed. Histology revealed grade 2 papillary transitional cell carcinoma of the bladder with no invasion into the lamina propria (G2pTa TCCB).

DISCUSSION: We recognise through our literature review that paediatric bladder cancers are not commonly reported in the UK. In our paper we highlight the relevant major studies that have been carried out world-wide, the reported incidence so far and gaps in the evidence base.

CONCLUSION: Despite the dearth of data about paediatric bladder malignancies there is enough case-based evidence, from world-wide sources, to support that bladder cancer must be suspected in the event of macroscopic haematuria. Ultrasound and cystoscopy are the standard diagnostic tools for bladder tumours. Endoscopic resection of the tumour followed up by interval ultrasound scans and flexible cystoscopy checks remain the mainstay of treatment hitherto.

1. Introduction

Bladder cancer below the age of 20 years old is not only rare, with an approximated total of 125 cases being collected worldwide by 2010 [1] but it has also been defined as clinico-pathologically distinct from bladder tumours in older age groups [2]. The majority are low grade superficial transitional cell carcinomas and are associated with a low rate of recurrence [3].

As benign causes of frank haematuria are more common in this age group than tumours, this often leads to a considerable delay in the diagnosis [2]. According to the literature, there are time delays of up to 1 year or more from initial onset of symptoms to diagnosis, in more than a quarter of cases [2]. It is understandable that clinicians have a low index of suspicion in this group of patients when a study like that conducted by Greenfield et al., showed that only 3 children/young adults (all aged less than 20) out of 342 who presented with frank haematuria were eventually diagnosed with bladder tumours [4]. There is also less inclination to expose young people to a general anaesthestic to perform a cystoscopy and possibly causing urethral trauma. However, this important diagnosis should not be missed or delayed and we would like to raise clinicians' index of suspicion for bladder cancer in the under age 20 group who present with haematuria and thus achieve the best prognostic outcomes.

2. Case report

Our patient was a healthy Caucasian 18 year old female high school student, who had never smoked, had not been exposed to industrial chemicals and drank minor quantities of alcohol (5 units per week on average). Her only previous medical history was mild asthma and a paraumbilical hernia repair aged 6. There was no history of early onset cancers in the family. She was sexually active at the time of the presentation and was a keen sportswoman, who belonged to the local football team.

She presented to her general practitioner (GP) after having had 2 discreet episodes of visible haematuria over a 2 week period. She also had some non-specific intermittent abdominal pains at the time, which she had not likened to menstrual type period pain. Her last menstrual period had been 3 weeks prior and there was no history of dysuria or trauma.

Physical examination was unremarkable and a urine dipstick showed no signs of infection, it was only positive for blood. The GP

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Table 1
Summary of the evidence.

Paper reference number and year	No of cases	Age of patient or age range of patients	Symptoms	Method of diagnosis/treatment	Histopathology	Follow up time and incidence of recurrence/prognostic information
[1] (2010)	6	<18 years/M:F = 4:2	Haematuria, pyelonephritis	Ultrasound, cystoscopy/endoscopic resection	G1 TCC G1-G3 TCC	No recurrences (1.5–5 years) mean 3.2
[3] (2010)	140	12–18 years/M:F = 2:1	Haematuria	Ultrasound, cystoscopy/endoscopic resection	Papillary urothelial neoplasm % of low malignant potential (PUNLMP) = 50.7% Rhabdomyosarcoma = 36.4	30 year study. Conditional survival calculated for 1 and 2 years after disease diagnosis was 93.6% and 97.5% 5-year survival rates were 50–80% over 30 years
[16] (1989)	2	15–20 years	Haematuria	Unavailable	Low grade TCC	No recurrence
[17] (1992)	1	8 year, female	Symptoms of appendicitis	Ultrasound, endoscopic resection	Grade 1 TCC	No recurrence
[18] (2001)	5	13–20 years	Frank haematuria and in the women, also recurrent cystitis	Pelvis USS, urogram, urine cytology and endoscopic resection	Grade 1 TCC and papillomas	No recurrence Average 41 months follow up 1st year: urinary cytology and cystoscopy every 3 months 2nd year: urinary cytology every 3 months and cystoscopy every 6 months in the 2nd year 3rd year: urinary cytology and bladder ultrasound every 6 months and cystoscopy every year. In a 13-year-old patient- annual cystoscopy check-up under general anesthesia in the first 3 years, and in later year, urinary cytology and bladder ultrasound every year.
[19] (1999)	1	19 years, male	Frank haematuria and bladder irritative symptoms (frequency, dysuria and urgency)	Incidental finding during cystolithotomy	TCC, grade 2 with invasion of lamina propria	Patient lost to follow up
[20] (2005)	23	4–20 years	Frank painless haematuria	Ultrasound, cystoscopy/endoscopic resection + mitomycin C	2 papilloma, 10 PUNLMP, 8 low grade papillary urothelial carcinoma (PUC), 3 high grade PUC	0.5–13 years (mean 4.5) 0 recurrence
[21] (2014)	1	9, male	Frank painless haematuria	Ultrasound and CT urogram/endoscopic resection	PUNLMP	16 months, no recurrence
[22] (1996)	5	11–18, all males	Frank haematuria	Ultrasound, urine cytology and cystoscopy	Papilloma, 2 grade 1 TCCs, 2 grade 2 TCCs. Superficial to lamina propria	0.7–6 years (mean 3.5) 1 recurrence
[23] (2014)	1	16, female	Frank haematuria	Ultrasound and cytoscopy	Low grade TCC	Repeat TURBT after 2 months revealed no persistent abnormal cells
[24] (2014)	1	13 year old male	Frank haematuria and concomitant appendicitis	Ultrasound, CT and subsequent endoscopic resection at the time of appendicectomy Mitomycin C.	papillary TCC, TaG1 stage	No recurrence at 18 months
[25] (2014)	8	<18 years	Haematuria	Ultrasound and cystosocpy	TCC. Two G1Ta, one G1T1, one G2T1, and five G2Ta. one patient had 2 small tumours, the rest were single lesions	8–27 years (mean 15 years). No recurrences
[32] (2014)	1	16 year old male	Painless frank haematuria	Ultrasound, urine cytology and cystoscpy	Low grade TCC, Ta	14 months, no recurrence

Table 1
(Continued)

Paper reference number and year	No of cases	Age of patient or age range of patients	Symptoms	Method of diagnosis/treatment	Histopathology	Follow up time and incidence of recurrence/prognostic information
[33] (2014)	1	5 year old male	Painless haematuria	Ultrasound, urine cytology, partial cystectomy and 5 rounds of intravesical BCG	HIgh grade TCC, no muscle invasion	21 months, no recurrence
[34] (2013)	17	<20 years (only 3 patients under age 10)	Frank haematuria predominate symptoms. Some patients had associated abdominal pain and a small percentage associated with urinary tract infections (UTIs)/recurrent UTIs	Ultrasound and cystoscopy	1 patient had high grade invasive urothelial carcinoma. The rest were low-grade papillary urothelial tumours, including PUNLMP and low grade PUC	Recuurences reported in this age group but specific details about these patents in the study not reported in the paper
[35] (2013)	1	4 year old male	Frank haematuria	Initial endoscopic resection and then subsequent partial cystectomy and adjuvant chemotherapy (methotrexate, vinblastine, Adriamycin, cisplatin) once re currence occurred	Malignant, high-grade, urothelial bladder carcinoma	Tumour quickly recurred after initial resection
[36] (2012)	1	9 year old, female	Gross haematuria	Ultrasound and endoscopic resection	Low grade TCC	No recurrence after 4 years

sent the patient for a urinary tract ultrasound scan which reported "an echodense polypous lesion present on the right side of the bladder wall measuring 21 × 15 × 17 mm" and on receipt of this report, was referred urgently for a Urology review. As is routine in the NHS for suspected cancer, the patient was seen within 2 weeks of referral by a urologist.

A microscopy and culture test of her urine confirmed her urine to be sterile and urine cytology was negative for aberrant cells. An initial diagnostic flexible cystoscopy showed a 2 × 2 cm raised lesion and some surrounding erythematous patches nearby. A staging CT urogram showed no evidence of any upper tract abnormality, lymph nodes or metastases.

Rigid cystoscopy and transuretheral resection of the bladder tumour were carried out soon after. The tumour was a unifocal 2 cm × 2 cm pedunculated bladder lesion, which was resected down to muscle in its entirety. Additional random bladder biopsies were also sent for histology.

Histology revealed grade 2 papillary transitional cell carcinoma of the bladder with no invasion into the lamina propria (G2pTa TCCB). It was confirmed that the lesion was unifocal as all other biopsies came back negative. After a multi-disciplinary discussion of her case, she was subsequently treated with a course of intravesical mitomycin C.

A relook flexible cystoscopy at 3 and 6 months has shown no signs of recurrence and she will continue to be followed up as an outpatient in the regular surveillance programme. Genetic mapping has also not revealed any predisposing genetic factors.

To our knowledge this is the first report of a British female in the under 20s age group, who has been diagnosed with low grade TCC and subsequently treated with intravesical mitomycin C.

3. Literature review

3.1. Method

The papers gathered for this literature review were generated by multiple database searches (Medline, Pubmed and EMBASE) using the following keywords/terms: bladder, urothelial, transitional, neoplasm, carcinoma, cancer, young, children, pediatric, child, paediatric, childhood, adolescent, less than, under, 20, twenty, teenage from 1946 to 2014. In order to be comprehensive, we also reviewed the literature published or cited by well known medical organisations such as the National Cancer Institute, the European Association of Urologists (EAU), the British Association of Urological Surgeons (BAUS) and the World Health Organisation (WHO).

We specifically wanted to look at papers that concentrated on bladder cancers in the zero risk population group and in the under 20s age group. In the literature search results, there were a number of papers that have cited children having had previous gastrointestinal augmentation cystoplasty as a risk factor for later developing a bladder malignancy [5–7]. A higher incidence of bladder cancers has also been noted in children who have previously received chemotherapy for tumours and haematological malignancies [8,9]. Any case reports concerning patients with these known predisposing factors for bladder cancer were also excluded as we felt that this cohort of patients should be categorised as 'high risk' regardless.

There were no other search limits used or filters applied. Any citations found not to be available in full paper format, either online or in hard copy format, were excluded [10–14].

4. Results

In total the literature search produced a range of papers, ranging from single case reports and case series to national epidemiolog-

Table 2
Simplified WHO/ISUP 2004 histological classification of urothelial tumuors (modified from [34]).

Noninvasive urothelial neoplasm		Invasive urothelial carcinoma
Papillary type	Non papillary type	
Urothelial papilloma, including inverted type Papillary urothelial neoplasm of low malignant potential Low-grade papillary urothelial carcinoma High-grade papillary urothelial carcinoma	Urothelial carcinoma in situ	

ical case studies. A summary of the papers is collated in Table 1. Most of the reported cases have come from large epidemiological studies conducted in North America, such as the Surveillance, Epidemiology and End Results (SEER) study [3] and from the WHO/International Society of Urological Pathology (ISUP) consensus classification report [15].

The SEER program was a 30 year long data collection study that included many contributing health facilities from all over North America. The health facilities reported new cases of cancer to a single database and the government run SEER program analysed the data. The authors were able to determine incidence rates of different histological bladder malignancies according to sex, age group and race. Over a 30 year period they only identified 140 cases, of which transitional cell carcinoma (TCC) was the most common in the age group 12–18. There was a 2:1 male to female case ratio [3].

With regard to the UK, there have only been a few sporadic cases of bladder cancer reported and the male:female ratio seems to be similar at ~3:1 [1].

Most of the case studies found defined their cohort of young patients as being younger than 40 due to epidemiological reasons but as it has become apparent with time that the under 20s age group are clinico-pathological different from older patients, more studies have started to collect data from this age group specifically. Currently there is a lack of data regarding best treatment for these patients and also follow up intervals and length of time.

5. Discussion

5.1. Aetiology

The aetiology of bladder cancer in the under 20s age group is poorly understood. Although in the older age group, environmental factors such as cigarette smoke, naphthalene dye, chemicals used in the rubber industry, bladder stones and schistosomiasis have been identified as significant risk factors. However, these environmental agents generally do not have much relevance to children and adolescents. The inconsistency of environmental factors and the early onset of the disease suggest that there is a genetic predisposition in these patients but as yet paediatric bladder cancers have not been found to be associated with aberrant genetic characteristics [28–30]. It is also unclear as to why there is a male preponderance for the disease.

5.1.1. Clinical presentation

Every case presented with frank haematuria and a small percentage of cases also reported abdominal pain [17,24,35] or symptoms of irritative bladder [1,18,19,35]. Ultrasound has proven to be a very sensitive test for picking up bladder tumours in young people, unlike in the older age group, where it can be more unreliable [30]. Urine cytology did not aid the diagnosis in a single reported case and this has been purported to be because most of the cases are low grade [2]

5.1.2. Management

Management thereafter also appears to be quite uniform, with almost all cases having a single diagnostic and curative bladder tumour resection (Table 1). Partial cystectomies have only been carried out in high grade cases [33,36] and where anatomically it was reported to be difficult for adequate endoscopic resection [33].

With regard to adjuvant chemotherapy however, there is a lot of variation as to whether it is used and how it is administered. There is no evidence base about the use of intravesical BCG in the under 20s age group as yet and the decision making is based on the histopathology grading and staging of the bladder cancer [20,24,33]. Only one paper has reported the use of MVAC (Methotrexate, Vinblastine, Adriamycin and Cisplatin) [35]. As the rates of recurrence seem to be so low in general, this supports the current trend to hold off using adjuvant chemotherapy in this age group and avoid further invasive treatment and its side-effects [33]. However, the evidence regarding prognosis is currently too weak for any solid recommendations to be made.

5.1.3. Prognosis and follow-up

The lack of detailed, consistent prognostic information also makes it unclear as to how these patients should be followed up. Clinicians want to avoid instrumenting a young bladder and causing more urethral trauma than is necessary but at the same time, detect recurrences early. Most centres across the world seem to use cystoscopy ±ultrasound ±urine cytology for follow up but none have been brave enough to suggest when these patients can safely stop being followed up. Reassuringly, the few long term follow up studies that have been carried out show that recurrences are very unusual in the under 20 years old group [1,2,17,20,25]. However, it can be argued that vigilant follow up is required based on a small proportion of cases that do get a recurrences, even in the low grade TCC group [22,34,35]. Over the 30 year study period of the SEER program, 5 year survival rates in these patients widely ranged from 50–80% [3]. It would be worthwhile repeating this study to get more concurrent results.

After analysing the literature, two apparent reasons for a lack of prognostic information can be offered. Firstly, the histopathological reporting classification system was last overhauled in 2004 by the World Health Organisation (WHO) [3,26,27] (Table 2). Therefore, even though the overwhelming majority of the literature report that patients under the age of 20 usually present with low grade superficial bladder cancers with no spread [2] the histopathological minutiae have only really been agreed upon in the last decade. A re-examination of the cases in the study conducted by Fine et al. [20] has shown that 10 patients (44% of the cohort) who would have been diagnosed with papillary urothelial carcinomas, using the old system, were actually graded as PUNLMP. New long term follow up studies are required, according to age of the patient and the classification of the tumour.

This brings us to the second reason, which is that up until recently, what is considered a 'young' person diagnosed with bladder cancer has been ill-defined. The majority of case studies have

focussed on the under 40s group and the data from children and adolescents has not been studied specifically. Now that it is becoming apparent that the under-20s age group is clinico-pathologically different from their older cohort [34], this information can be targetted.

6. Conclusion

This case was investigated and treated smoothly without much delay but there is potential for other cases to be missed or their diagnosis to be delayed because clinicians have a low index of suspicion in this age group. This case report and literature review highlights the significance of haematuria in the low risk paediatric group and its association with bladder malignancies. Evidence so far shows that the majority of cases are very treatable and have good long term survival statistics but we are lacking data to make firm recommendations as to the optimum management plan in the under-20's and their follow-up. In the UK and Europe, it would be prudent to setup a large cancer registry to look at bladder cancer in the under 20s and have a standardised way of collecting and reporting the data with these specific questions in mind.

Conflicts of interest

No conflicts of interest to declare.

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Author contribution

Miss Lisa Sheehan, MBBS BSc (Hons) MRCS: Wrote the case report, carried out the literature search and analysed the papers and wrote up the literature review.

Mr Adeel Anwar: Edited the paper, helped to analyse the literature review results.

Mr Sashi Kommu: Encountered the case, Reviewed the paper and help to edit.

Consent

I can confirm consent has been obtained.

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