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Acquired childhood bladder melanosis

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Abstract

Background: Bladder melanosis is rare. It has previously been described only in the fifth decade of life or beyond; it has not been described in childhood. Previous descriptions have generally been case reports, and so the natural history is poorly understood. Urinary symptoms present at the time of cystoscopy have frequently been attributed to bladder melanosis. A possible suggested aetiology is aberrant migration of melanocyte migration during embryogenesis.

Case presentation: We present the first case of bladder melanosis in a child. He had been under our care since the age of 5 years with urinary incontinence and at that time, had undergone cystoscopy demonstrating normal bladder mucosa. A diagnosis of idiopathic detrusor overactivity with underactive voiding had been made. After other unsuccessful treatments, intravesical botulinum toxin was proposed. At the age of 13, repeat cystoscopy prior to botulinum toxin, demonstrated widespread pigmented areas in the bladder mucosa. Histology showed bladder melanosis. Our finding is important for several reasons. This is the first reported case of bladder melanosis to affect a child. The previous normal cystoscopy in our patient would refute the explanation that bladder melanosis is a congenital condition. Furthermore, the development of melanosis on the background of stable symptoms raises the possibility that the condition may be asymptomatic.

Conclusions: This unique finding of bladder melanosis in a child has provided further insight into this rare and poorly understood condition.

Keywords: Childhood, Bladder, Melanosis

Background

Bladder melanosis is a rare condition, first described in 1986 [1]. To date, the condition has been described only in adults over the age of 40 years. We describe the first case of melanosis in a child.

Case presentation

Our patient presented in 2011 at the age of 5 years with symptoms of day- and night-time urinary incontinence. He had a single episode of frank haematuria. Ultrasound demonstrated a solitary right kidney. In the absence of other explanations for his haematuria, he underwent cystoscopy. This confirmed a single right ureteric orifice but otherwise normal urethra and bladder.

His urinary incontinence was challenging to manage. He underwent protracted treatment and investigation. Of note, he was found to have an abnormal bladder residual due to underactive voiding, but otherwise, videourodynamics were unremarkable. He did not respond to urotherapy, desmopressin, antimuscarinics (tolteridine, solifenacin), beta 3 agonists (mirabegron), or transcutaneous electric nerve stimulation (TENS). He even learnt clean intermittent catheterisation (CIC). CIC had been recommended five times a day, but in practice was performed twice a day. By the time of his cystoscopy in 2019, he had been performing CIC for 34 months. Ultimately, ambulatory urodynamics demonstrated detrusor overactivity. He and his family agreed to intra-vesical botulinum toxin treatment. During this, he started treatment with fluoxetine for severe anxiety and reached a BMI of 43.8.

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In 2019, at the age of 13 years, he was taken to theatre for his first intra-vesical botulinum toxin treatment under general anaesthesia. At cystoscopy, we were surprised to find that the bladder had extensive patches of pigmented mucosa interspersed amongst the normal mucosa (Fig. 1). This pigmentation did not extend into the urethra. Cold-cup biopsies were taken, and a decision was made not to proceed with botulinum toxin treatment.

Biopsy of the bladder tissue showed dark pigment within epithelial cells as well as fibroblasts and macrophages in the lamina propria (Fig. 2). The epithelium was otherwise normal with no dysplasia. Melanocytes were not seen. There was no evidence of fungal infection or melanoma. The specimens were negative for S100 and HMB45 immunostaining. The pigment stained black with Masson-Fontana (Fig. 3), in keeping with melanin.

Bladder melanosis was present and unchanged on subsequent cystoscopies, performed to administer botulinum toxin, up to 29 months later.

Discussion

Bladder melanosis was first described less than 40 years ago [1]. Since then, there have been only case report descriptions. A review article in 2014 described only 16 cases in the literature up until that time [1]. To our knowledge, there have been only another six cases reported subsequently [2–6].

The diagnosis of melanosis is based on histology findings. The finding of golden brown or dark granules has a differential that includes melanin, lipofuschin, and haemosiderin. Lipofuschin is most commonly found in lysosomes as a product of membrane degradation and is rich in lipids. Lipofuschin is stained by periodic acid-Schiff stain and Zeihl-Neelson staining and has been documented in patients on long-term ciprofloxacin. Haemosiderin is derived from the breakdown of haemoglobin and is stained by Perl's Prussian blue stain. Melanin is seen as golden yellow-brown pigment intracellularly and extracellularly on light microscopy. Melanin is bleached by acid and reduces the ammonia silver nitrate solution in Fontana-Masson stain, to give a black colour.

The origin of melanin in the bladder in this condition is difficult to explain. Normal bladder urothelium does not contain melanocytes or melanosomes. It is suggested that the melanin granules are produced by melanocytic cells that either underwent aberrant migration from the neural crest during embryogenesis or were derived through aberrant differentiation of urothelial stem cells [7]. Melanocytes can be detected using melanocytic markers such as MelanA, S-100, and HMB45 which are antigens on the melanocyte. MelanA is detected by antibodies such

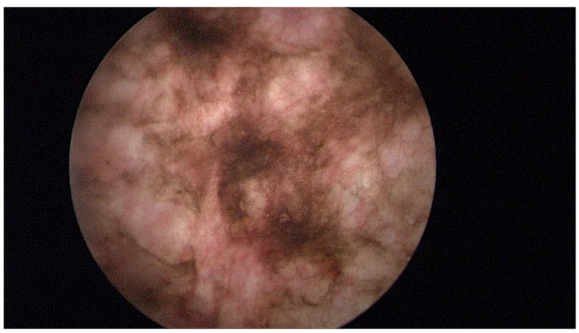

Fig. 1 Bladder melanosis cystoscopic image. Black pigmentation of bladder mucosa noted at the time of cystoscopy, involving the entire bladder

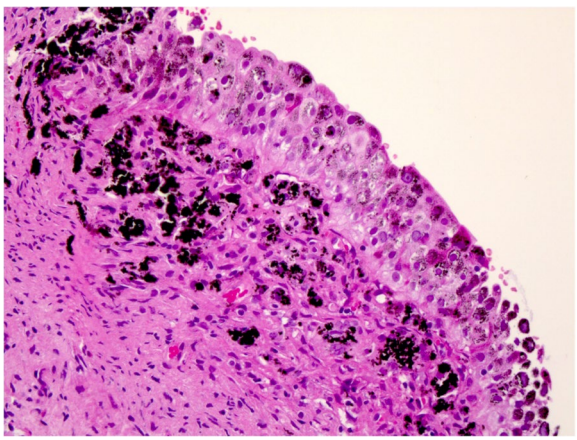

Fig. 2 High-power view of bladder mucosal biopsy. Melanin is seen in the transitional epithelium and in the fibroblasts in the lamina propria on H&E staining

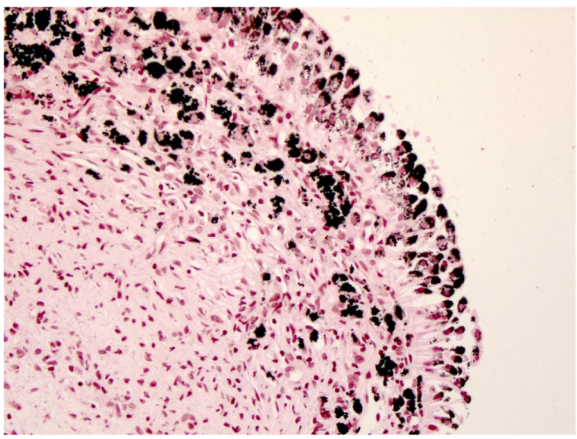

Fig. 3 Fontana-Masson stain of bladder mucosal biopsy. Melanin is stained black with the stain and helps to diagnose bladder melanosis

as A103 and M2-7C1; Pmel 17 antigen is detected with HMB-45 monoclonal antibody. S-100 is another immunohistochemical protein found in melanomas [8]. All melanomas may not show all the markers, but this does not affect their clinical course or prognosis. These markers have not been detected on biopsy specimens [2, 9]; hence, melanocytes are not found in cases of bladder melanosis.

The clinical significance of bladder melanosis is also uncertain. Of those described in the literature, 6 were associated with haematuria, 5 with symptoms of LUTS, 7 with UTI or cystitis, 5 with incontinence, 2 with voiding difficulties, 1 with renal calculi, and 2 with abdominal pain. Some patients had a combination of the above symptoms. Three of the patients with haematuria were associated with bladder malignancy.

There have been 4 patients reported to have malignancy associated with the finding of bladder melanosis. In 2 of these patients, melanosis was found with concurrent urinary tract malignancy with bladder transitional cell carcinoma (TCC) in one and ureteric and renal TCC in the other [3, 10]. Both of these patients presented with haematuria. Another patient was found to have bladder TCC 1 year after the original discovery of bladder melanosis [11]. She presented originally with recurrent UTI, at which time the biopsy demonstrated melanosis. A year later, she developed haematuria, and repeat cystoscopy disclosed high-grade superficial TCC. The final documented case of malignancy with bladder melanosis was in a woman who had extensive melanosis of the vulva, vagina, and bladder in association with melanoma of the vulva [12]; she was subsequently found to have melanoma within the bladder and vagina.

The clinical course of the above patients is not mentioned in the case reports. Most of the patients in the papers are in their eight decades of life. Three patients who had TCC have been under surveillance and were well. In only one case where a man in his 50s presented with obstructive symptoms due to urethral stricture, a resolution of melanosis was seen once the stricture was treated. Some authors have attributed the symptoms and even predisposition of malignancy to melanosis. However, the case reports tended to be descriptions of point incidence, rather than serial bladder examinations, and so the natural history of the condition has only been speculated on. All patients who have been found to have bladder melanosis will by definition have had symptoms; whilst the prevalence of bladder melanosis in the wider asymptomatic population is unknown, it is therefore possible that bladder melanosis is an incidental finding at cystoscopy performed to investigate other problems.

There is limited information on the natural history of melanosis. There is a single previous case report of a patient who developed melanosis after a previous normal cystoscopy [2]. This is particularly interesting as the authors report there was a subsequent spontaneous resolution of the bladder melanosis. In another patient where the melanosis was resected, there was no subsequent recurrence [13].

Our patient is important in several respects. This is the first description of bladder melanosis in a child; all other descriptions of bladder melanosis have been in adults over the age of 40 (range 43–86 years) [9]. Furthermore, this is only the second case of acquired bladder melanosis. This would suggest it is unlikely that melanosis arises from neural crest migration during embryogenesis. Another important consideration is that melanosis occurred during the presence of symptoms that he has had at the time of his first initial and negative cystoscopy; this would suggest that the melanosis has not contributed to symptoms but have developed after the symptoms were present. This would support the view that bladder melanosis may be an asymptomatic and incidental finding.

It may be asked whether melanosis developed in this patient as a result of his treatment. None of the medications he has taken has been associated with pigment deposition. It is difficult to imagine that the extremely low current that is used with TENS therapy can trigger melanin deposition. Intermittent catheterisation is very unlikely to have been a trigger; the distribution of melanosis in the bladder was widespread and not favoured to areas of the bladder mucosa that a catheter may have damaged. Intermittent catheterisation is widely performed by many of our patients undergoing cystoscopy, and we have not seen even a mild variant of melanosis in them.

Our view is that melanosis has not contributed to symptoms in our patient. We would favour an interpretation that melanosis may be asymptomatic and that it is possibly discovered incidentally during the investigation of coexisting symptoms.

A final consideration is the reaction of the patient and parents to the cystoscopy findings. The patient and parents were distressed at the report of the cystoscopy appearance. The novelty of the finding and the wait for the histology results were difficult; it exacerbated the child's pre-existing anxiety. We hope that by providing this report, we may allow surgeons encountering a similar situation to provide a better reassurance to their patients whilst histology is awaited.

Conclusion

This is the first description of bladder melanosis in a child. This is only the second case demonstrating that melanosis is acquired. The development of melanosis on

the background of unchanged urinary symptoms suggests that the condition may be asymptomatic.

Abbreviations
TCC: Transitional cell carcinoma; TENS: Transcutaneous electric nerve stimulation.

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Authors' contributions
RV is the corresponding author and involved directly in the management of the case and collecting of the data with reviewing the literature and writing the case report. MA is the histopathology consultant who helped in understanding and presenting the histopathology findings. AT is the supervising consultant with a direct contribution to the writing of the paper. All authors have read and approved the manuscript.

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Declarations

Ethics approval and consent to participate
Ethics committee approval is not necessary for case report publication.

Consent for publication
Written consent taken from the parents.

Competing interests
The authors declare that they have no competing interests.

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