African Journal of Urology

CASE REPORTS Open Access

Non-functional bladder paraganglioma in a patient with complex hematological disorders: case report

Dragos Puia[1,2*] and Catalin Pricop[1,2]

Abstract

Background: Although bladder cancer is quite a common cancer, most common encounter being transitional cell carcinomas, paragangliomas with such localization, is a very rare histopathological finding. In addition, hematuria in a patient with a theoretically "hypercoagulable" condition is uncommon; in our case it was the single symptom.

Case presentation: We report the case of a 44-year-old female referred to our hospital for gross hematuria. The CT scan revealed an intraluminal enhancing bladder mass. Also, the XIII coagulation factor level was 36% and surprisingly genetic mutations suggesting inherited thrombophilia were found: MTHFR C677T negative, A1298C positive and PAI-1 gene polymorphism (675 4G/5G). The hematologist recommended folic acid 5 mgs daily. A TURBT was performed (macroscopically no residual tumor tissue). The immunohistochemical examination revealed tumor cells intensely positive to chromogranin and synaptophysin, negative for cytokeratin AE1/3, p63, 7, 20 or CDX2, and slight (less than 5%) positive for Ki-67. The combined examinations correspond to a bladder paraganglioma. Six months after surgery, the patient had no clinical symptoms and no relapse sonographically and cystoscopically.

Conclusions: Although a very rare entity, bladder paraganglioma should be suspected in patients with hematuria and unexplained hyperadrenalism symptoms such as hypertension, serious dizziness, headache or palpitation. The immunohistochemical examination is important not only for diagnosis but also for identifying the functionality of the tumors. In such cases the therapeutic management could be different as in transitional cell carcinomas.

Keywords: Bladder cancer, Inherited thrombophilia, Paraganglioma, Case report

1 Background

Bladder cancer is the ninth most common cancer worldwide, with an increased incidence from 430,000 new cases diagnosed in 2012 to 550,000 in 2018 [1]. Although the majority of bladder tumors are transitional cell carcinomas (TCC), less than 10% are not TCCs. The most frequent non-TCCs cancers are represented by squamous cell carcinoma, adenocarcinoma, urachal cancer, small cell carcinoma, lymphoma and different types of sarcoma-like leiomyosarcoma, rhabdomyosarcoma or angiosarcoma. Paragangliomas are rare tumors of neural crest origin, which can be benign or malignant; although histopathological diagnosis is difficult, we did not found in literature association with coagulation factor XIII deficit.

2 Case presentation

A 44-year-old female was referred to our department for gross hematuria 1 week before admission to the hospital. The patient had no medical history and no chronic medication. She denied smoking and also any exposure to solvents or asbestos. On admission, the physical examination did not reveal any eruptions or swelling of joints or superficial lymph nodes; blood

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pressure and pulse rate were also normal. The abdominal ultrasonography did not show other abnormalities except urinary bladder full with echogenic material (blood clots).

The laboratory findings revealed: white blood count 8900/μL, serum hemoglobin 7.6 g/dL, hematocrit 22.5%, serum creatinine 0.82 mg/dL and C-reactive protein of 21 mg/dL; the other routine blood tests were within normal limits. After bladder blood clots were evacuated, an enhanced computed tomography scan was performed (Fig. 1). It revealed an intraluminal enhancing bladder mass. No other abnormalities regarding the kidneys or the intra-abdominal solid organs were found, and also no lymphadenopathy was revealed. Because the hematuria was very severe, related to the possible bladder tumor etiology, a hematological examination was performed. The XIII coagulation factor level was 36%, and surprisingly genetic mutations suggesting inherited thrombophilia were found: MTHFR C677T negative, A1298C positive and PAI-1 gene polymorphism (675 4G/5G). The hematologist recommended folic acid 5 mgs daily.

A transurethral resection of the bladder tumor (TURBT) was performed (macroscopically no residual tumor tissue). Because the histopathological examination (Fig. 2) could not properly confirm the diagnosis of bladder tumor, immunohistochemical examination was performed.

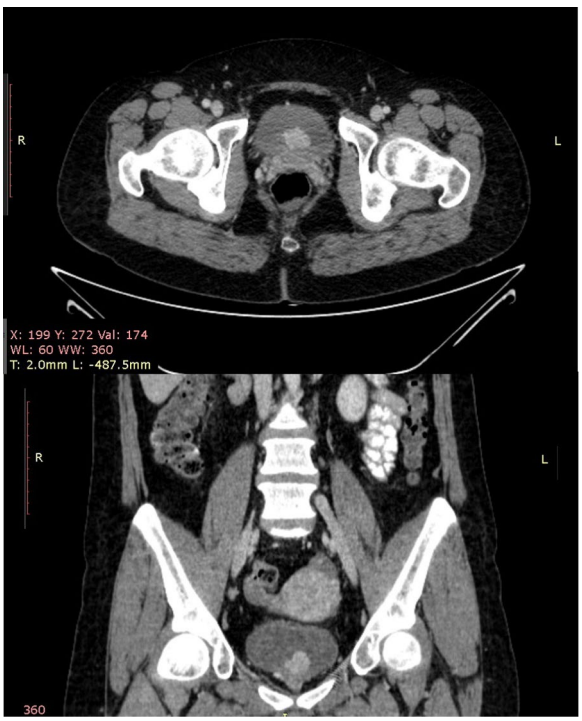

Fig. 1 CT scan showing an intraluminal bladder mass

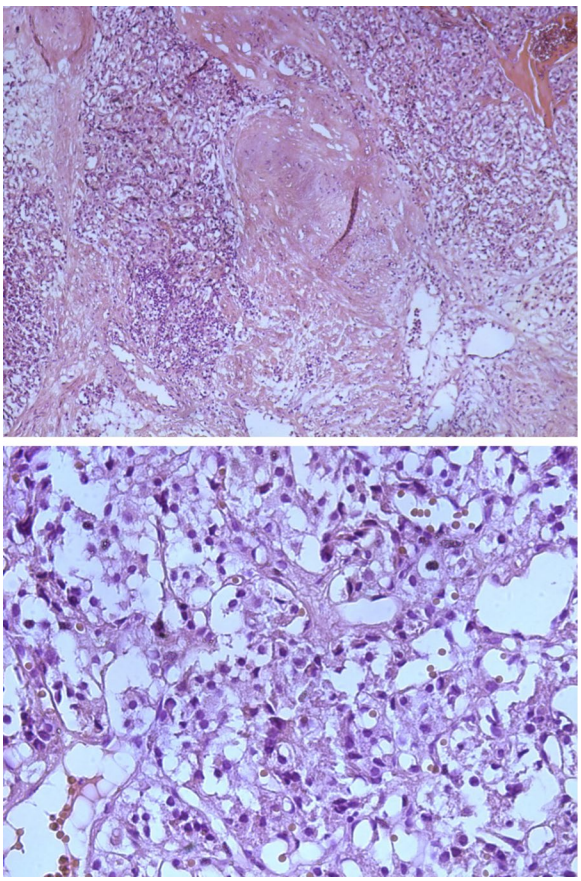

Fig. 2 Histopathological examination with hematoxylin and eosin staining

The immunohistochemical examination revealed tumor cells intensely positive to chromogranin and synaptophysin, negative for cytokeratin AE1/3, p63, 7, 20 or CDX2, and slight (less than 5%) positive for Ki-67. The combined examinations correspond to a bladder paraganglioma (BP). Six months after surgery, the patient had no clinical symptoms and no relapse sonographically and cystoscopically.

3 Discussion

The first case of urinary BP was reported in 1953 by Zimmerman et al. in a 74-year-old woman [2]. The epidemiology is still debatable; according to Pastor-Guzmán et al., bladder paragangliomas are very rare and represent 6% of the paragangliomas and 0.06% of all bladder tumors, while Chen reported that 85% of extraadrenal paragangliomas are located below the diaphragm, from which 10% was in the bladder [3, 4].

BP could be divided according to their clinical characteristics into two types: functional and non-functional. Usually, the diagnosis of a functional paraganglioma is often obtained thanks to its clinical manifestations; in

our patient, the clinical presentation was not suggestive. According to Siatelis et al. in 90% of the paraganglioma patients, elevated blood pressure, serious dizziness, headache, profuse sweating and palpitation appear; in our case, severe hematuria was the only symptom [5]. We explain this by her XIII factor deficiency because thrombophilic patients have an increased risk for the development of venous thromboembolism, acute myocardial infarction or ischemic stroke, while our patient had no such medical history. Besides these clinical manifestations, according to Deng et al., these patients should also have elevated plasma or urinary catecholamines and positive reaction for metaiodobenzylguanidine or octreotide scintigraphy [6]. All this is absent in the cases of non-functional tumors.

In the absence of hyperadrenalism symptoms, clinical diagnosis is difficult. The histological diagnosis is also difficult; according to Ginesu et al., the differential diagnostic is made with meningiomas, schwannomas, hemangiopericytomas, melanomas and various metastatic carcinomas [7]. When the tumor is located in the bladder, histological characteristics are similar to the most common bladder cancers and thus misdiagnosed as urothelial carcinoma. According to Zhou et al. microscopically, the paraganglioma appears as cells with a 'zellballen' pattern with abundant eosinophilic or amphophilic cytoplasm divided by delicate vascular stroma. Fortunately, the diagnostic is suggested through immunohistochemical examination, the tumor being positive for neuro-specific enolase, synaptophysin and chromogranin and negative for cytokeratins [8].

The main therapy for localized BP is complete resection because this type of tumor is insensitive to both chemotherapy and radiotherapy. TURBT and laser resection are mainly used for the treatment of BPs at stage T2. Because some authors like Jurincic [et al.] are claiming that it is very difficult to completely resect using TURBT, partial cystectomy could be recommend [9]. When the tumor is located in the trigone of the urinary bladder or/and has extensive infiltration into adjacent tissues, a radical cystectomy may be performed. According to Liu et al., the factors that could indicate a high probability of malignancy of the BP are CgA expression, Ki67 > 3%, karyokinesis > 1/10 HPF and/or atypical karyokinesis, confluent necrosis, and appearance of aneuploidy [10]. Considering that our patient had Ki-67 < 5%, karyokinesis < 1/10 HPF and no confluent necrosis, we had treated as a tumor with low chances of malignancy and cystectomy was not performed. There are no guidelines regarding the duration of follow-up and the data in the literature are conflicting. While Beilan et al. suggested that follow-up is not necessary in patients with benign and localized BP, Katiyar et al. recommend a long-period follow-up even in non-functional tumors [11, 12].

To our knowledge, there are no data in the literature that correlate paraganglioma with inherited thrombophilia or coagulation factor XIII deficit, although Hill and Kitamura encountered disseminated intravascular coagulation in patients with pheochromocytoma [13, 14].

4 Conclusions

Although a rare entity, BP should be suspected in patients with hematuria and unexplained hyperadrenalism symptoms such as hypertension, serious dizziness, headache or palpitation. The immunohistochemical examination is important not only for diagnosis but also for identifying the functionality of the tumors. For localized tumors, complete resection of the neoplasm could produce a manageable oncological outcome, especially in non-functional paragangliomas.

Abbreviations

BP: Bladder paraganglioma; TCC: Transitional cell carcinomas; TURBT: Transurethral resection of the bladder tumor.

Acknowledgements

Not applicable.

Author contributions

DP directed the care of the patient and contributed to draft of the paper and acquisition and analysis of the medical information. CP reviewed the literature and did the critical review of the paper. All authors have read and approved the manuscript.

Funding

The authors declare that this study has received no financial support.

Availability of data and materials

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Declarations

Ethics approval and consent to participate

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors have declared that no competing interests exist.

Human and animal rights

The authors we have declared that regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association have been followed.

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Received: 4 April 2022 Accepted: 1 August 2022
Published online: 19 August 2022

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