Peer Review File

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Reviewer A

The authors have reported on three cases of malignant priapism and have provided a review of the available literature. It is important to report these cases as it is such a rare entity. The authors ultimately conclude that management is a case by case basis but present a possible algorithm for management.

- For readers, I think it would be important to further expound upon the diagnosis of malignant priapism as it is a rare entity. The algorithm starts with a clinical suspicion for malignant priapism, but with its low incidence, many physicians would likely manage as a typical priapism with blood gas and irrigation/aspiration and/or phenylephrine. Case 1 mentions penile pain for 2 weeks, which often in ischemic priapism, would not persist for that long secondary to fibrosis - would time be an additional factor to increase suspicion along with history of malignancy?

- We appreciate this comment. Time of onset has not been found to be a consistent indicator differentiating malignant vs traditional ischemic priapism. Though uncommon, delayed presentations can be seen in both entities and thus we did not include time as an indicator of malignant priapism.

- Should shunts overall be avoided in malignant priapism or is that the case secondary to a glanular malignant lesion in case 2? Are blood gases necessary in malignant priapism if therapeutic penectomy is the recommendation?

- Many thanks for your consideration. Our stance regarding treatment was to proceed from a more conventional therapy standpoint to more aggressive procedures such as penectomy. Despite necrosis in case two after shunting, we still lack sufficient data to rule out its effectiveness in every case. There have been reports that indicated shunting provided temporary pain relief. The statement regarding incomplete resolution of detumescence and pain following shunting has been added to page 6 line 239. “However, there have been cases which shunting resulted in temporary pain relief and incomplete resolution of erection that ultimately required total penectomy.”
We believe that obtaining blood gas is a necessary step in determining the etiology of the priapism considering that not all priapisms in cancer patients may arise from the malignant pathology.

- Case 3: did the MRI not indicate spread to the corpora cavernosa and this was only picked up by Pet CT? There is no mention of pain relief from the surgery
Do the authors advocate early penectomy?

Thank you for the comment. The patient's MRI was obtained before his priapism and thus did not show cancer invading the corpora. This was seen on subsequent PET scan which has been added as image two.
The pain attributed to malignant priapism was resolved after penectomy. This statement has been added to page 4 line 106
Our experience shows that penectomy results in pain relief and is helpful to the overall condition of the patient. However, we should bear in mind that these patients are already experiencing numerous difficulties and performing a radical procedure such as penectomy should be reserved as a last-step solution. Given the current data, less aggressive methods such as palliative radiotherapy have shown promising results in some cases. Therefore, we propose the stepwise approach mentioned in the algorithm to be a logical method according to the available documents.

- Can alternative therapies be further commented on?

Thank you for your comment. An additional explanation on hormonal therapies which have been used in treating priapism has been added to page 5 line 202. "Hormonal therapies including antiandrogens, GnRH agonists and 5α-reductase inhibitors are also an emerging modality of treatment in priapism patients. However, their effectiveness in such advanced cases of malignant priapism is yet unknown."

Reviewer B

The authors describe a rare but devastating problem in urology. I recommend formatting Case 3 similarly to Cases 1 and 2 (2-3 separate paragraphs). Excellent flow chart and treatment algorithm, which emphasizes an individualized approached.

Many thanks for your comment. The third patient description is now formatted as you requested.

Reviewer C

nice paper but please include some of the mri pictures for all cases

Thank you for your meticulous attention. MRI scan has been added for patient 1(page 3 line 107) and PET scan was available for patient 3(page 4 line 151).

Reviewer D

I would like to congratulate the authors due to well-summarized cases and comprehensive review of this rare clinical phenomenon. Furthermore, they provide a treatment algoritihm for

malignant priapism management which is can not find a place in current American or European guidelines and will be helpful for providers.
I should indicate one concern about this manuscript;
The first sentence in introduction “Malignant priapism, defined as metastasis to the penis causing clinical priapism, is a rare disease with approximately 500 reported cases to date.” should be revised. Because malignant priapism is not only caused from metastasis, but also caused by primary malignancies of penis as indicated by authors in further parts of them manuscript.

Many thanks for your comment. This sentence on page 2 line 61 has now been updated as you advised. We have now indicated that malignant priapism arises from both primary involvement and malignancy.

Reviewer E

The authors present a case series of 3 patients with malignant priapism all palliatively treated with penectomy. This is an interesting case series highlighting the role of penectomy is symptom control for these unfortunate patients. This is a very frustrating process to treat with a highly variable pathophysiology due to the uniqueness of each patients malignancy. Penectomy often seems extreme in these men, but I have also been pleasantly surprised by the degree of symptom control in these patients. I commend the authors for reporting their experience on this challenging problem that is extremely hard to study. This work is a valuable contribution.

Major Comments:

1. For case 1 and 2 the authors only briefly mention each patient had a prolonged erection. Please provide more details on duration of erection, whether it was constant or intermittent, exam findings such as how rigid it was, was a mass palpable, etc. Due to the heterogeneity of malignant priapism and varying pathogenesis, it is important to understand these details.

- Thank you for this comment to improve the paper. We have added additional details as requested to cases 1 (page 3 line 90) and 2 (page 3 line 115)

2. For case 1 it is stated MRI confirmed metastatic disease...and associated malignant priapism. This suggests priapism was diagnosed off of the MRI findings. However, priapism is usually diagnosed off exam, history, blood gas, and potentially duplex US. Can the authors please clarify this statement, if there were MRI findings suggestive of priapism those are important details to add but should not suggest diagnosis was made off MRI.

Thank you for the comment. We believe that this may just be a misunderstanding of how it is written. He had a mass in the penis diagnoses with MRI but priapism was not diagnosed from

MRI. The diagnosis was more based off of physical exam and corporal blood gas as described.

3. Case 2-the blood gas is not strongly indicative of ischemic priapism, the pH is not terrible and the O2 is fairly normal for penile blood gas. More data is needed to clarify the etiology, what was the appearance of the blood of aspiration, duration of priapism, was it intermittent and the blood gas was obtained during a period where the patient was not ischemic? It is also stated that the cavernosal arteries were patent on duplex US, if this was an ischemic priapism you would not expect to see inflow and patent arteries. Please provide more details on timing of these studies and clarify the findings. Further I find the necrosis experienced following distal shunt interesting. This suggests an arterial inflow problem but the cavernosal arteries were patent. Were there any pertinent findings on the dorsal arteries? These details will help readers understand the pathogenesis in greater detail of this rare problem.

Many thanks for your attention. The blood gas has was taken after an initial aspiration. The initial aspirate was very dark and consistent with ischemia but the 2nd specimen was less so likely as there was some refilling. Also, the blood flow was measured more proximally on the ultrasound while the shunt is distal. This has been updated in the text in page 3 line 120.
We believe the reason for the necrosis to be the rapidly progressing cancer growth that prevented healing. This statement has been added to page 6 line 238.

4. Discussion-please add in discussion of hormonal therapies. I realize the authors did not use these at all and these may be somewhat controversial, however, some advocate for hormonal therapies in these men and it would round out the discussion to have some commentary of the data behind these therapies.
Many thanks for comment. An additional explanation regarding hormonal therapies in treating priapism has been added to page 5 line 202. However, we have noted that the role of hormonal therapy in treating malignant priapism is unknown.

Minor Comments

1. Introduction-line 70-71 has two incomplete sentences which can be combined.
   We thank you for your valuable comment. The mentioned sentences have now been combined.
2. Introduction-the focus is on metastatic tumors causing malignant priapism, however local invasion of perineal sarcomas or penile malignancies can also cause it. Please mention this as well.
   I would like to thank you for your comment. This statement on page 2 line 61 has now been updated as you advised.