Int J Clin Exp Pathol 2021;14(1):45-53
www.ijcep.com /ISSN:1936-2625/IJCEP0114949

Original Article

Metastatic prostatic adenocarcinoma to the brain and spinal cord: a contemporary clinicopathologic analysis of 30 cases

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Received May 25, 2020; Accepted June 29, 2020; Epub January 1, 2021; Published January 15, 2021

Abstract: Metastatic prostatic adenocarcinoma (PCa) to lymph nodes and bone is well documented in the literature, however only case reports and small series of metastatic PCa to the brain and spinal cord with clinicopathologic analysis have been published. We identified 30 cases of metastatic PCa to the brain and spinal cord. The mean patient age was 67 years (range: 50 to 87 years). Thirteen (43%) cases involved the brain and 17 (57%) cases involved the spinal cord. Most of the cases (60%) were a single mass. Of the 13 cases involving the brain, the temporal lobe 6 (46%) was the most common site and the spinal cord lesions involved the thoracic region in 13/17 (76%) cases. All patients had one or more metastases to other organs. In 8 patients, the brain or spinal cord metastasis was the initial diagnosis of PCa. In the patients that had prior prostate biopsy specimens available, the Gleason score ranged from 3+3=6 (Grade group 1: indicating unsampled higher grade PCa) to Gleason score 4+5=9 (Grade group 5). Follow-up was available in 21 cases with a mean duration of 20 months (range: 1 to 130 months). This is one of the largest clinicopathologic studies to date of metastatic PCa to the brain and spinal cord. Although rare, metastatic PCa should be considered in the differential diagnosis of a solitary brain or spinal cord mass in male patients, even over a decade after the initial diagnosis of PCa.

Keywords: Prostatic adenocarcinoma, metastasis, brain, spinal cord

Introduction

Worldwide, prostate cancer (PCa) is a leading cause of morbidity and mortality accounting for 7.1% of all new cancer cases and 3.8% of all cancer deaths in 2018, second only to lung cancer in men [1]. Because of early detection and advances in therapeutic intervention, the prognosis in most cases of PCa is improving, however metastatic PCa is still associated with a high morbidity and mortality in a subset of patients. The 5-year relative survival rate for PCa with distant spread (stage IV disease) is 31% compared to 98% for all stages of PCa [2]. Metastatic PCa to lymph nodes and bone is well documented in the literature, however only case reports and small series of metastatic PCa to the brain and spinal cord with emphasis on clinicopathologic analysis have been published. The frequency of central nervous system (CNS) metastasis in patients with PCa is not well characterized, with estimates of frequency of brain metastasis ranging from 0.2-2% of patients, a significant proportion of which are only identified at autopsy [3]. The spinal cord, and specifically the epidural space, is a more common site for CNS metastasis and many CNS cases may either be missed or never diagnosed. Therefore, a substantial number (up to 10%) of patients with PCa may develop CNS metastasis in the course of their disease [4].

There is very limited contemporary data regarding the clinicopathologic characteristics of CNS metastasis of PCa. In this study, we reviewed the major clinicopathologic characteristics of patients with metastatic PCa to the CNS.

Materials and methods

A search was made through our Urologic Pathology and Neuropathology files, and consult

cases for patients with metastatic PCa to the brain and spinal cord from 2001 to 2019. Patient demographics, clinical presentations, radiologic features, location, focality, and size of CNS metastases, and available follow-up information were obtained. Hematoxylin and eosin (H&E)-stained sections and available immunohistochemical stains of selected case were reviewed. Statistical analysis was performed. This study was completed following the guidelines of and with approval from Emory University Institutional Review Board.

Results

We identified 30 cases of metastatic PCa to the CNS including intraparenchymal (intra-axial) and meningeal based (extra-axial) lesions (**Table 1** and **Figure 1**). Cases that involved lesions that were limited to the bone (skull or spine) without involving the brain and spinal cord and/or the meninges were excluded.

Twenty-seven cases were from the routine in-house surgical pathology/neuropathology services within our institution and 3 cases were from the expert consultation services with limited clinical information. Twenty-nine cases were from neurosurgical resection specimens, and 1 case was from an Autopsy.

Patient demographics

The mean age of the patients at the time of diagnosis of CNS metastasis was 67 years (range: 50 to 87 years). Fifteen patients identified as Caucasian or White, 12 identified as African American or Black, and the racial designation of three patients was not reported (**Figure 1**).

Clinical presentation

Clinical history was available for 27 of the 30 patients (**Table 1**), and almost all patients were symptomatic when they presented with CNS metastasis. The most common neurological presentation was back pain and lower extremity weakness for patients with spinal cord metastasis and altered mental status for patients with brain metastasis. Other presenting signs/symptoms included third cranial nerve palsy, eye pain and drooping, one-sided weakness, paresthesia, speech difficulty, persistent headache, chest pain, bowel and bladder incontinence, and constipation. The time interval between presentation with CNS metastasis and initial diagnosis of PCa was up to 14 years. In 8 patients, there was no prior diagnosis of PCa and in 5 cases the CNS presentation occurred within 1 year of diagnosis of PCa. One of the patients was on active surveillance for a period of eight years prior to presenting with CNS metastasis. In the patients that had prior prostate biopsies samples available for review, the Gleason scores ranged from 3+3=6 (Grade group 1: likely indicating unsampled higher grade PCa) 2/13 (15%) to Gleason score 4+5=9 (Grade group 5) 5/13 (40%), including a subset that had extraprostatic extension and seminal vesicle invasion in their corresponding radical prostatectomy specimens. As expected, cribriform glands and intraductal spread was present in the majority of the cases with Grade group 4 and 5 disease. Twenty-eight (93%) patients had documented metastases to other sites including bone, lymph nodes, bladder, perirectal/perianal tissue, penis, lung, liver, and adrenal gland. Within this cohort, bone was the most common additional site of metastasis.

Follow-up was available in 21 patients with a mean duration of 20 months (range: 1 to 130 months). All patients had androgen deprivation therapy following neurosurgical resection as applicable, and all but 2 patients received radiation therapy. Six patients died of disease or other causes, and 6 patients were referred to hospice care.

Features of CNS metastasis

The distribution of the CNS metastasis is presented in (**Table 1** and **Figure 1**). Thirteen (43%) cases were intracranial and 17 (57%) cases involved the spinal cord. Most of the cases (60%) were a solitary mass within the cranium or spinal cord. Of the 13 intracranial cases 7 were dural metastases, 4 were parenchymal, 1 involved the pituitary and in 2 cases the location (dural vs parenchymal) was not provided. The temporal lobe was the most common site of intracranial metastasis occurring in 6 (46%) of the cases (**Figure 2A-D**), followed by the occipital lobe with 3 (23%) cases, the frontal lobe with 2 (15%) cases, and the parietal lobe with 1 (8%) case. Two of the 3 occipital lobe cases also involved another location (pari-

Table 1. Clinicopathologic data of patients

Patient	Age (yrs)	Race	Pre-CNS metastasis Prostate biopsy/ Resection findings	Clinical presentation	Location of CNS metastasis	Treatment received and follow up
1	70	N/A	GS/GG N/A	Brain mass	Brain, right temporal	Brain mass excision (f/u N/A)
2	52	Black	GS 4+4=8 (GG4) ADT, RT and CTX	Back pain and left leg weakness PCa with bone metastasis (1 year before CNS presentation)	Spine, Thoracic, epidural	Spinal cord mass excision (f/u for 3 months)
3	84	N/A	GS/GG N/A ADT	Symptoms of cord compression History of hormone independent PCa	Spine, Cervical, epidural	Spinal cord mass excision (f/u N/A)
4	71	Caucasian or White	GS 3+3=6 (GG1) ADT and RT	Back pain and progressive lower extremity weakness/paresthesia PCa (7 years prior to CNS presentation)	Spine, thoracic, epidural	Spinal cord mass excision, bilateral Orchiectomy, RT, and CTX (f/u for 28 months)
5	57	African American or Black	GS/GG N/A	Lower extremity weakness PCa (4 years prior)	Spine, cervical, epidural	Spinal cord mass Excision and ADT (f/u for 130 months)
6	75	African American or Black	No prior history of PCa	Cranial nerve III palsy, left eye pain and drooping	Brain, pituitary	Pituitary mass excision (transphenoidal microsurgical adenectomy), ADT, and RT (f/u 2 months, died)
7	66	Caucasian or White	No prior history of PCa	Mid back pain and lower extremity weakness	Spine, thoracic, epidural	Spinal cord mass excision, ADT and RT (f/u N/A)
8	57	African American or Black	GS 4+5=9 (GG5) RT (palliative to spine and pelvis)	Acute altered mental status and seizures PCa (1 year prior)	Brain, right temporal, dural	Brain mass excision (f/u N/A)
9	65	African American or Black	GS/GG N/A ADT	Hormone-refractory metastatic PCa (9 years prior)	Brain, right parietal and occipital, dural	Brain mass Excision. Died following surgery
10	64	N/A	GS/GG N/A	N/A	Brain, left temporal, NOS	Brain mass excision (f/u N/A)
11	67	Caucasian or White	GS 4+4=8 (GG4) Radical prostatectomy GS 4+5=9 (GG5) pT3bN0 ADT and RT	Thoracic myelopathy, bowel and bladder incontinence Hormone refractory PCa (radical prostatectomy 12 years prior)	Spine, thoracic, epidural	Spinal cord mass excision, RT and CTX (f/u for 13 months)
12	87	Caucasian or White	GS/GG N/A ADT and RT	Progressive bilateral lower extremity weakness PCa (7 years prior)	Spine, thoracic, epidural	Spinal cord mass excision, ADT and RT (f/u for 38 months)
13	50	Caucasian or White	GS4+5=9 (GG5) RT (Salvage)	Intractable nausea and vomiting as well as vision loss and balance issues, and altered mental status PCa, radical prostatectomy (2 years prior)	Brain, right frontal and occipital	Brain mass excision, RT (f/u available for 3 months, then hospice)
14	60	African American or Black	GS/GG N/A	Right temporal abscess PCa with lung metastasis	Brain, right temporal, intra-axial, dural	Brain mass Excision. (f/u N/A) Transferred to hospice
15	73	African American or Black	No prior history of PCa	Lethargy and left sided weakness found to have a massive right intracerebral hemorrhage	Brain, right temporal	Spinal cord mass excision. DOD
16	60	African American or Black	GS 4+4=8 (GG4) ADT	Bilateral extremity weakness and urinary retention PCa (5 years prior)	Spine, thoracic, epidural	Spinal cord mass excision, ADT, and RT (f/u for 32 months. Died from shock)
17	70	Caucasian or White	GS 4+4=8 (GG4) ADT, CTX, and RT	Leg, back and pelvic pain PCa (3 years prior)	Spine, lumbosacral, epidural	Spinal cord mass excision, RT (Palliative) (f/u for 3 months, opted for hospice care)
18	69	Caucasian or White	GS 4+4=8 (GG4) ADT and RT	Intermittent speech difficulties and headache PCa (2 years prior)	Brain, left parietal, subdural	Brain mass excision, RT (f/u for 19 months and then referred for to hospice for palliative care)
19	71	Caucasian or White	GS 4+3=7 (GG3) RT and Cryoablation	Altered mental status PCa (14 years prior)	Brain, right frontal, dural	Brain mass Excision (f/u for 3 month)

20	55	African American or Black	No prior history of PCa	Acute onset of lower extremity weakness and numbness	Spine, thoracic, epidural	Spinal cord mass excision, ADT, and RT (DOD 3 month after surgery)
21	71	African American or Black	No prior history of PCa	1 week of bilateral lower extremity paralysis	Spine, thoracic, epidural	Spinal cord mass excision, ADT, and RT (f/u 37 months)
22	63	Caucasian or White	GS/GG N/A ADT and RT	Chest pain and bilateral leg weakness PCa (1 year prior)	Spine, thoracic, epidural	Spinal cord mass excision (f/u 1 month)
23	69	African American or Black	No prior history of PCa	Altered mental status with associated aphasia	Brain, left occipital,	Spinal cord mass excision and RT (f/u 3 months)
24	73	Caucasian or White	GS 3+3=6 (GG1)	Left sciatica and back pain PCa (8 years prior, on active surveillance)	Spine, lumbar, epidural	Spinal cord mass Excision, ADT and RT (f/u 20 months)
25	76	Caucasian or White	GS 4+5=9 (GG5) Radical prostatectomy GS 4+3=7 (GG3), tertiary pattern 5. pT3aN0 RT, ADT	Acute onset of bilateral lower extremity weakness, multiple falls and inability to walk (PCa diagnosed 7 years prior)	Spine, thoracic, epidural	Spinal cord mass excision, ADT and RT (f/u for 22 months, significant decline and referred to hospice)
26	67	Caucasian or White	No prior history of PCa	Loss of consciousness and seizures. PCa (metastatic)	Brain, right temporal	Brain mass excision, RT, CTX, and ADT (f/u 18 months)
27	63	Caucasian or White	GS 4+5=9 (GG5) ADT and RT	Worsening thoracic back pain and right lower extremity weakness PCa (4 years prior)	Spine, thoracic, epidural	Spinal cord mass excision, ADT, RT and CTX, (DOD: f/u 9 month)
28	60	African American or Black	GS/GG N/A RT, ADT, and CTX	Progressive bilateral lower extremity weakness, back pain and constipation. (PCa 6 years prior)	Spine, thoracic, epidural	Spinal cord mass Excision, and ADT (f/u 7 months up)
29	64	Caucasian or White	GS 4+5=9 (GG5) ADT and RT	Persistent headache (PCa 1 year prior)	Brain, right cerebellum	Brain mass excision, ADT, and RT (f/u 25 months)
30	69	African American or Black	No prior history of PCa	Back pain	Spine, thoracic, epidural	Spinal cord mass excision, ADT, and RT (f/u 8 months)

Abbreviations: ADT-Androgen deprivation therapy; CTX-chemotherapy; DOD-died of disease; f/u = follow up; GG: Grade group; GS = Gleason score; N/A: not available; PCa = prostate cancer; RT-radiation therapy.

etal and frontal lobes). One case mimicked a brain abscess, another case a subacute subdural hematoma and two other cases presented as intracerebral hemorrhagic lesions. Of particular interest was a metastasis to the pituitary gland (**Figure 3A-F**) initially thought to be a pituitary adenoma and another case presenting as a cystic cerebellar (posterior fossa) lesion on imaging (**Figure 4A-D**), both of which presented as single metastasis further confounding the differential. Nine of the 13 (69%) cases were on the right side of the brain including cerebellum, in contrast to 3 (23%) cases on the left side (No lateralization for the pituitary lesion).

The spinal cord lesions involved the thoracic region in 13 of 17 (76%) cases (**Figure 5A-C**). The cervical and lumbar spinal cord were each involved in 2 (12%) cases and the sacral spinal cord was involved in 1 (6%) case that also involved the lumbar spinal cord. All the spinal cord lesions were epidural in location and 14 (82%) involved adjacent vertebrae. Five (29%) of the spinal cord cases demonstrated multifocal epidural metastases.

Histopathologic features

Most of the lesions were intraparenchymal and/or dural-based and the tumor excision specimens were often admixed with blood, bony fragments, and necrotic tissue. Histopathologic examination showed metastatic carcinoma involving the CNS tissue with microscopic features consistent with metastatic adenocarcinoma from a prostate primary site, including enlarged, hyperchromatic nuclei and prominent nucleoli (**Figures 2A**, **2B**, **3A**, **3B**, **4A**, **4B**, **5A** and **5B**). The Gleason score of the metastatic tumors ranged from 4+4=8 (Grade group 4, 6%) to 5+5=10 (Grade group 5, 56%). There

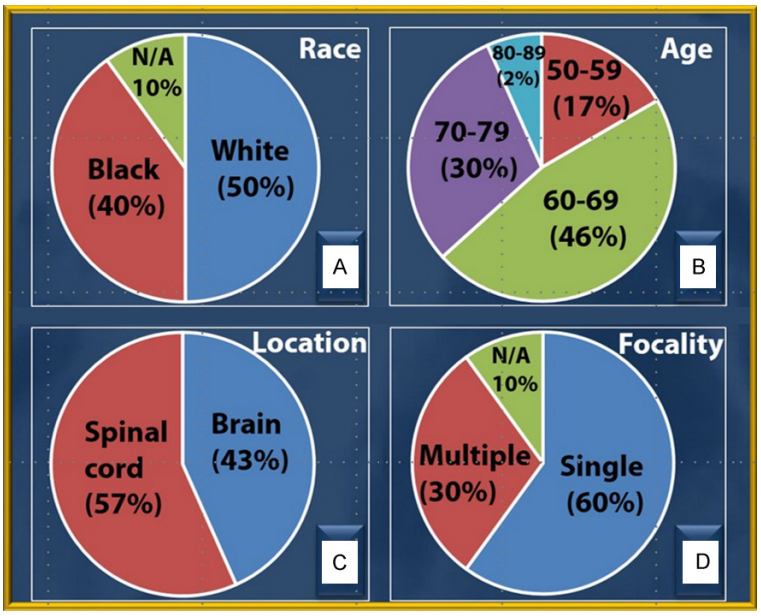

Figure 1. Pie charts showing. (A) Racial distribution of patients; (B) Age distribution of patients; (C) Location of lesion(s); (D) Number of foci of lesion(s). (N/A = not available).

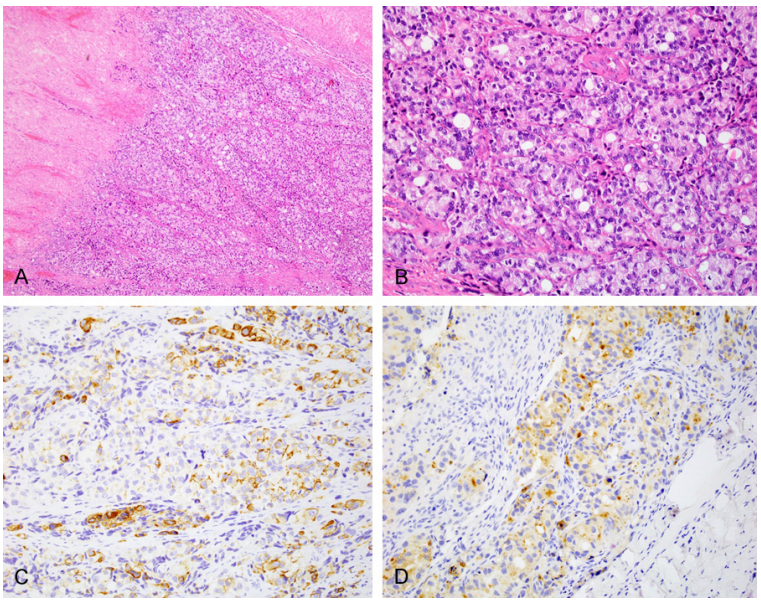

Figure 2. Histopathologic features of prostatic adenocarcinoma with right temporal lobe metastasis. (A and B) H&E (4× and 20×), (C) AE1/AE3 (20×) and (D) PSAP (20×).

was no direct correlation between the Gleason score (Grade group) on the prostate needle core biopsies and that of the metastatic tumor, further emphasizing the pitfalls associated with unsampled tumor on biopsies in the few patients that initially had low grade tumors. In a subset of cases, prior history of PCa and immunohistochemical stains were helpful to confirm the diagnosis in view of the fact that the neoplastic cells appeared poorly differentiated and infrequently showed obvious glandular differentiation. The histopathologic features in some cases were non-specific and raised the differential diagnosis of other metastatic tumors and benign entities such as pituitary adenoma and neurenteric cyst in a couple of cases. Expression of cytokeratins and prostatic specific markers were utilized in most cases to confirm the diagnosis of metastatic PCa. Other markers su ch as synaptophysin, chromogranin, GFAP, CDX2, TTF1, Na psin, CD138 and S100 were also performed in some cases, to exclude metastasis from other common primaries or to rule out other differential diagnoses.

Discussion

Although bones and lymph nodes are the commonest sites of metastasis for PCa, CNS metastases also occur [5]. In our series involving 30 patients with CNS metastasis from PCa, there was a slight racial predisposition towards Caucasian/White population. The mean and median age at presentation of CNS metastasis in this series was 67 years and most of the patients (46%) were in the 60-69-year age group. This is similar to the mean age of 66 years at diagnosis for PCa, and the median age of 64 years at diagnosis for brain parenchymal metastases in a clinical and autopsy-based study performed at the MD Anderson Cancer center [6, 7]. The age range of 50-87 years in this study was similar to the age range of 50-85 years in another retrospective review of a single institution, although the median age of 73 years in their study was higher [8].

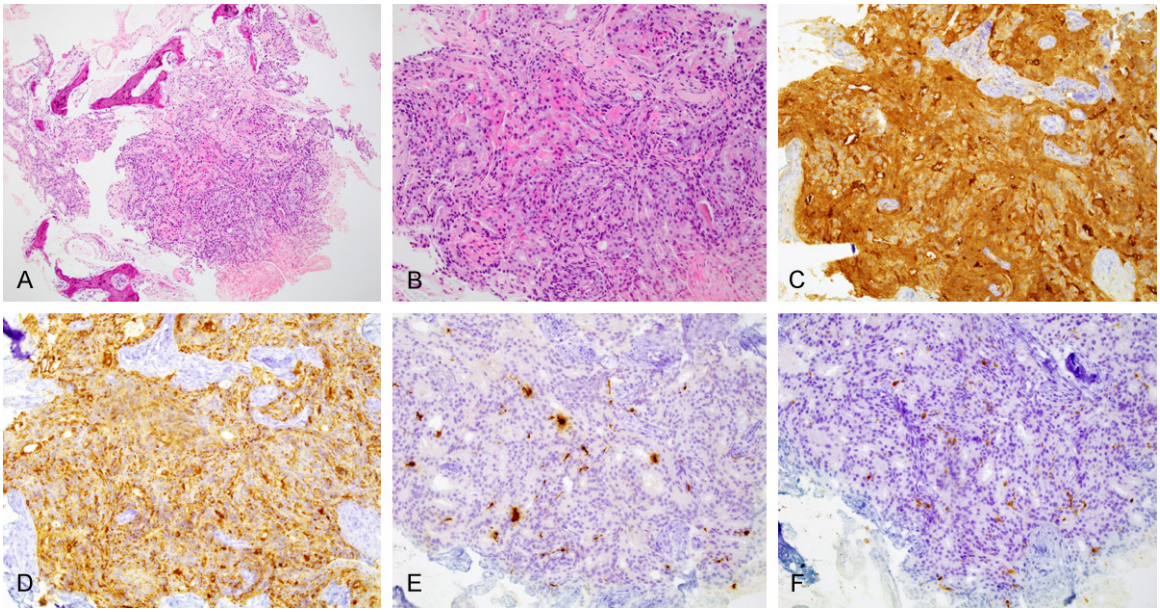

Figure 3. Histopathologic features of prostatic adenocarcinoma with pituitary metastasis. (A and B) H&E (10× and 20×), (C) PSA (20×), (D) PSAP (20×), (E) Chromogranin (20×) and (F) Synaptophysin (20×).

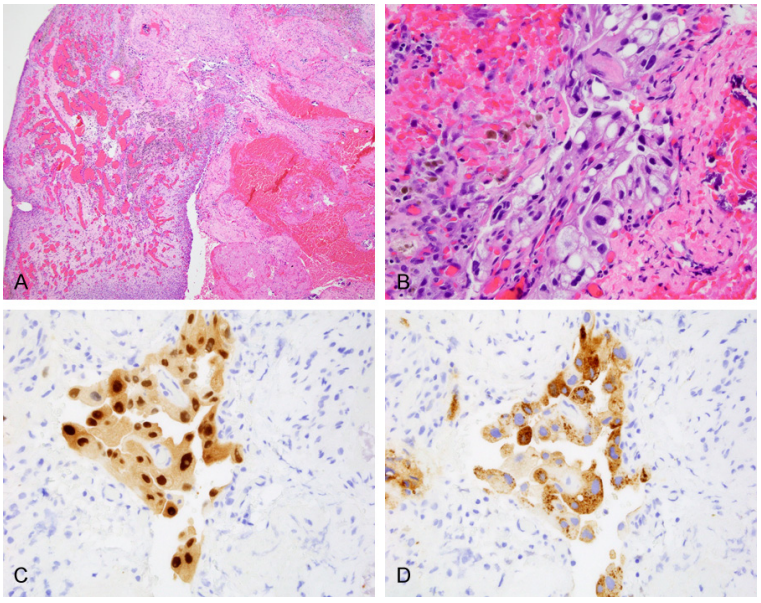

Figure 4. Histopathologic features of prostatic adenocarcinoma with cerebellar metastasis. (A and B) H&E (4× and 40×), (C) NKX3.1 (40×) and (D) PSA (40×).

CNS metastasis preceding the diagnosis of the primary tumor is very rare for PCa although there have been a number of case reports [3, 9-12]. Eight (27%) of our patients had no prior diagnosis of PCa and another five (17%) presented with CNS metastasis soon after diagnosis of PCa. These findings are similar to a recent study where the majority of patients presenting with PCa CNS metastasis had a prior diagnosis of primary PCa [13]. One can argue that CNS metastasis from PCa may not always manifest as a late presentation of the disease, but may instead correlate with a clinically more aggressive tumor and/or histopathologically poorly differentiated tumor [14, 15]. Recently, it was shown that metastatic PCa to the CNS demonstrates lower expression patterns of prostate tumor suppressors in a manner that is consistent with aggressive behavior of the tumor [16, 17]. CNS metastasis can also be the indication of relapse and was the site of relapse(s) of PCa in previous reports [18, 19].

Diagnosis of metastatic PCa to the CNS may be challenging especially when there is no prior history of PCa or when there is a solitary craniospinal lesion, as metastatic tumors are usually thought to present as multiple lesions. In one case report with a single large brain metastasis, the clinical and radiologic picture was also thought to be most consistent with a high grade

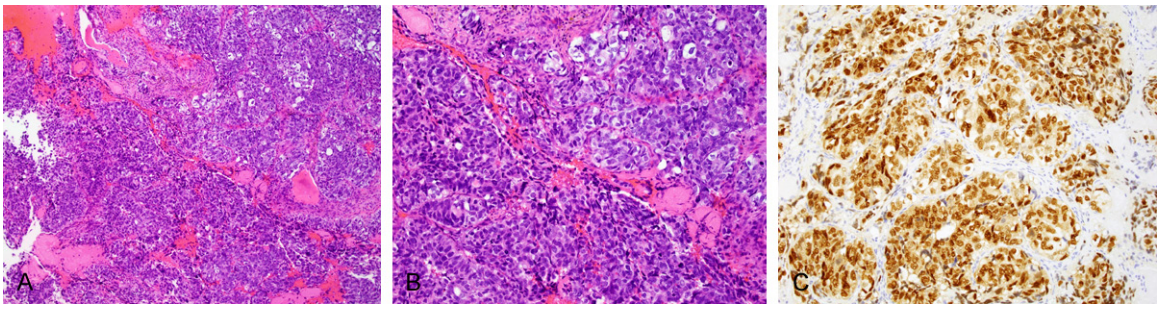

Figure 5. Histopathologic features of prostatic adenocarcinoma with thoracic spinal cord epidural metastasis. (A and B) H&E (10× and 20×) and (C) NKX3.1 (20×).

glioma [11]. Most patients with CNS metastatic PCa will have concurrent metastatic disease at other sites, especially the bone, as in our study, although a solitary CNS lesion without prior or concurrent metastases do rarely occur [20]. In this study, we also found the rare presentations of brain metastatic PCa as subdural hematoma, as well as cystic and hemorrhagic lesions [21-29].

The spinal cord is more common than the brain as the site for CNS metastasis from PCa and we found a predilection for the spinal cord over the brain (1.3:1). The thoracic spinal cord is the most common site for spinal epidural metastases for all systemic cancers, however one case report asserts that for PCa the lumbar spine is the commonest [9, 30]. In our study, the thoracic spinal cord/epidural space was overwhelmingly the most common site of spinal metastasis occurring in 13 (76%) cases while lumbar and cervical metastatic disease were each seen in only 2 (12%) of the cases. All the spinal cord lesions were epidural and no intramedullary PCa spinal lesions were present in this study. Intradural extramedullary spinal cord lesions of PCa is very rare with only seven reported cases and have a predilection for the lumbosacral region [31]. Intramedullary spinal cord metastatic lesions are exceedingly rare with only 4 cases reported in the literature; two of these involved the conus medullaris and in two of these cases there was no prior history of PCa [4, 32, 33].

The pituitary gland is an uncommon site for metastasis, and metastatic PCa to this location continues to pose diagnostic challenges. Five percent of all metastatic tumors to the pituitary are attributed to PCa, making PCa the fourth most common metastatic tumor to the pituitary, after breast, lung and gastrointestinal tumors [34]. In our study, the pituitary lesion presented in a patient with no prior history of PCa as third cranial nerve palsy and was initially thought to be a pituitary adenoma based upon imaging and clinical workup. However, following review of the permanent sections and immunohistochemical studies demonstrating a population of cells that was positive for both PSA and PSAP and negative for synaptophysin and chromogranin, the lesion was confirmed to be metastatic PCa. Over three decades ago, the first case of symptomatic PCa metastasis to the pituitary gland unassociated with sellar osseous disease was reported in a 61-year-old who presented with a 2-month history of increasing bifrontal headache and peripheral visual loss with no prior diagnosis of PCa [14]. A number of other case reports of metastatic PCa to the pituitary have been described including a collision tumor of metastatic PCa to a suprasellar meningioma in a patient with a 2-month history of progressive visual blurring, a normal PSA level, negative CT scans, essentially normal baseline pituitary hormones, and with a preliminary diagnosis of a pituitary macroadenoma or a suprasellar meningioma [16, 35-38].

In conclusion, this is the largest contemporary predominantly non-clinical/imaging/autopsy-based study to date on the clinicopathologic findings of patients with metastatic PCa to the CNS. Both clinicians and pathologists should be aware that PCa is variable in its presentation and progression. Late CNS metastases may occur, even over a decade after the initial diagnosis of PCa. Also, CNS metastases may be the first presentation of PCa and can mimic as other malignant or benign neurological process. A complete and thorough histopathologic

and immunophenotypic assessment of CNS lesions following surgical resection is essential to avoid the various potential diagnostic pitfalls.

Disclosure of conflict of interest

None.

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