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Case Study
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Paraneoplastic Sensorimotor Peripheral Neuropathy in Prostate Cancer

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Abstract

Background: Paraneoplastic Neurologic Syndrome (PNS) refers to the presence of cancer with non-metastatic or therapeutic manifestations of neurological disease. PNS has been attributed to tumor secretion of hormones, peptides, or cytokines or an immune response against the tumor.

Case Description: Here, we report a patient with gradual weakness of the lower extremities bilaterally. He underwent a transurethral resection of the prostate 2 years earlier. The pathology revealed a Gleason 9 poorly differentiated adenocarcinoma. Following 6 cycles of docetaxel and 3 months of abiraterone and prednisone, the patient started enzalutamide. On exam, weakness of the dorsiflexors of the ankles, quadriceps, and hip flexors were noted bilaterally. There was decreased pinprick sensation over the feet. The EMG/NCV confirmed a sensorimotor peripheral polyneuropathy of the upper and lower extremities. The patient declined any further medical testing or treatment and died 8 weeks later.

Conclusion: Neurosurgeons and neurologists should be aware of PNS in patients with prostate cancer who experience a sensorimotor peripheral polyneuropathy of the upper and lower extremities. EMG/NCV and antibody detection are valuable tools in confirming and treating this rare condition.

Keywords: Peripheral neuropathy; Paraneoplastic; Prostate cancer; Electromyography; Nerve conduction study

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Introduction

Paraneoplastic syndrome may occur in a patient with cancer which is not attributed to direct tumor invasion or compression, metastasis, or side effects due to oncological therapy [1]. Paraneoplastic syndrome has been reported in approximately 100 cases of prostate cancer as exemplified by endocrine, neurological, and dermatological conditions [1]. It is most commonly detected in small cell lung carcinoma although it has also been observed in lymphoma and breast, colon, uterine, prostate, and ovarian cancers [2,3].

Paraneoplastic Neurologic Syndrome (PNS) denotes the presence of a malignancy with the exclusion of other known causes of neurological symptoms [4]. PNS develops in approximately 6% of patients with cancer and is often associated with an advanced metastatic malignancy [1]. PNS arises from tumor secretion of hormones, peptides, or cytokines or an immune response against the tumor [1-4].

Here, we present a patient with prostate cancer who developed a sensorimotor peripheral polyneuropathy of the upper and lower extremities. This report emphasizes the need to perform EMG/NCV studies and antibody detection to verify PNS in prostate cancer.

Case Study

History and oncological treatment

An 81 year old man presented with a 1 year history of gradual weakness of the lower extremities bilaterally. He was initially able to ambulate with a walker which became more difficult due to buckling of the knee joints. He denied any low back pain or pain, numbness, or tingling of the legs. Past surgical history was significant for lumbar surgery 6 years earlier which resolved his low back pain. There was no history of diabetes mellitus.

The patient underwent a Transurethral Resection of the Prostate (TURP) 2 years earlier after

Table 1: Paraneoplastic peripheral neuropathy in prostate cancer in the literature.

Study	# of Patients	Type of prostate CA	Features	Positive antibody detection	Outcome after PNS diagnosis
Campbell et al. [7]	1	Adenocarcinoma	Symmetric mixed polyneuropathy	Not performed	Not specified
Baird et al. [6]	1	Small cell carcinoma	Sensorimotor peripheral neuropathy of UE and LE	Anti-Hu	Hormonal manipulation, partial improvement but still significant deficit
Venkatesh et al. [12]	1	Small cell carcinoma	Polyneuropathy of LE	Not performed	1 cycle paclitaxel and carboplatin (not tolerated, no improvement); patient died
Cowley et al. [3]	1	Adenocarcinoma	Sensory neuronopathy UE and LE	Anti-Hu	2 courses of methylprednisolone (no improvement); IV immunoglobulin (some improvement)
Storstein et al. [5]	3	Not specified	Sensorimotor neuropathy	Anti-CRMP5 (2);Anti-Yo (1)	Not specified
Choi et al. [2]	1	Adenocarcinoma	Sensorimotor peripheral neuropathy of UE and LE	Anti-Hu	Fentanyl patch, gabapentin, physical and occupational therapy; no functional improvement
Current study 2021	1	Adenocarcinoma	Sensorimotor peripheral neuropathy of UE and LE	Not performed since patient died after EMG/ NCT	Patient died without treatment after diagnosis of PNS

CA: Cancer; UE: Upper Extremities; LE: Lower Extremities; PNS: Paraneoplastic Neurological Syndrome

experiencing burning and difficulty with urination. The pathology revealed a Gleason 9 poorly differentiated adenocarcinoma. A bone scan showed intense abnormal activity in the left scapular body and cervical spine as well as a compression fracture of L1. A CT of the chest, abdomen, and pelvis 3 months after the TURP demonstrated multiple bilateral pulmonary nodules (maximum diameter 2.6 cm) and numerous hepatic metastases (maximum diameter 3.7 cm). The patient was treated with 6 cycles of docetaxel 75 mg/m^2 after which a chest CT demonstrated progression in the liver and lungs. The patient then started abiraterone 1000 mg and prednisone 5 mg daily. A thoracic and lumbar MRI with and without Gadolinium contrast demonstrated multiple compression fractures including a 60% loss of height of the T12 vertebral body as well as severe stenosis T12-L5 with compression of the cauda equina. A decompressive laminectomy was recommended which the patient declined due to his age and metastatic prostate cancer. The abiraterone and prednisone were discontinued after 3 months due to proximal muscle weakness. The patient subsequently started enzalutamide 140 mg daily 15 months after the TURP. CTs of the chest, abdomen, and pelvis with contrast at both 4 and 7 months after initiating enzalutamide revealed excellent responses. The patient had taken enzalutamide for 11 months when he underwent neurological evaluation.

Physical examination

On exam, weakness of the dorsiflexors of the ankles, quadriceps, and hip flexors were noted bilaterally. Patellar and Achilles deep tendon reflexes were symmetric but diminished bilaterally. There was decreased pinprick sensation over the feet and decreased vibration sense over the left ankle. Position sense was intact.

EMG/NCV of the legs

Needle EMG revealed fibrillations in the tibialis anterior, gastrocnemius, and quadriceps. Large polyphasic units were observed in the distal muscles, quadriceps, and tensor fascia lata. The peroneal nerves showed decreased motor conduction velocity bilaterally. No H reflex was recorded on stimulation of the tibial nerve bilaterally. No sensory potentials were recorded on stimulation of the plantar nerves bilaterally. The right superficial peroneal nerve showed low amplitude of sensory nerve action potentials, and no potential was recorded on the left. The right median and ulnar nerves demonstrated prolonged distal motor latency and low normal motor conduction velocity as well as prolonged sensory latency with low amplitude. The EMG/NCV confirmed a peripheral sensorimotor polyneuropathy predominantly involving the legs. The presence of large polyphasic units in the proximal muscles were thought to be related to the additional presence of lumbosacral radiculopathy.

Following the EMG/NCV, the patient declined any further medical testing or treatment. He died 8 weeks later after receiving hospice care.

Discussion

Of the 37 patients with PNS and prostate cancer reported in the literature, the most common isolated PNS was paraneoplastic encephalomyelitis/limbic encephalitis (n=10), paraneoplastic cerebellar degeneration (n=9), and subacute sensory neuronopathy (n=7) [5]. A total of 23 (62%) patients were positive for onconeural antibodies, with the anti-Hu antibody detected in 17 patients. Eighteen (49%) patients were diagnosed with prostate cancer prior to the PNS.

Only 8 patients with paraneoplastic peripheral neuropathy in prostate cancer have been described in the literature (Table 1) [2,3,6,7,10,12]. Three cases were prostatic adenocarcinoma, while two were small cell prostate cancer. The type of prostate cancer was not specified in 3 cases. Five cases exhibited a sensorimotor peripheral neuropathy. The anti-Hu antibody was detected in 3 cases, anti-RMP5 in 2 cases, and anti-Yo in 1 case. Antibody testing was not performed in 2 patients. It has been reported that symptoms associated with paraneoplastic syndrome often improve or resolve following treatment of the primary malignancy [1-3]. Myriad treatments were initiated after confirmation of PNS in the patients with paraneoplastic peripheral neuropathy in prostate cancer such as hormonal manipulation, cytotoxic chemotherapy, methylprednisolone, IV immunoglobulin, and gabapentin (Table 1). However, these interventions provided minimal or no improvement of the patients' PNS symptoms.

Docetaxel, a semi synthetic analogue of the antitumor agent paclitaxel, inhibits tubulin depolymerization [8]. In New et al. study of 186 patients receiving docetaxel in phase I or phase II studies, 21 (11%) patients developed mild to moderate sensory neuropathy, 10 of whom also developed weakness in the proximal and distal extremities while taking docetaxel [8]. The patient in the present case did not develop his leg weakness until 4 months after the docetaxel was discontinued. Therefore, we presume that this chemotherapy was not responsible for his peripheral neuropathy. Abiraterone significantly reduces androgen production by blocking the enzyme cytochrome P450 17 alpha-hydroxylase (CYP17) and is not associated with leg weakness [9]. This chemotherapy is often administered with prednisone, and the patient's proximal weakness was initially attributed to the prednisone. The abiraterone and prednisone were discontinued after 3 months, and his leg weakness progressed for the

next year at which time he underwent the EMG/NCV studies.

Enzalutamide is an oral androgen-receptor inhibitor that has been shown to significantly decrease the risk of radiographic progression and death as well as delay the initiation of chemotherapy in men with metastatic prostate cancer [11]. In a double-blind phase 3 study with 1,717 patients with metastatic prostate cancer who received enzalutamide or placebo, the most common side effects were fatigue, back pain, constipation, and arthralgias [11]. No correlation between enzalutamide and peripheral neuropathy has been observed. Interestingly, Choi et al. [2] described a patient with prostate cancer who developed peripheral sensorimotor polyneuropathy confirmed by EMG following treatment with enzalutamide 40 mg. Anti-Hu antibody reactivity was positive, and he was diagnosed with paraneoplastic syndrome caused by adenocarcinoma of the prostate.

Here, the patient experienced a peripheral neuropathy of the upper and lower extremities following the diagnosis of prostatic adenocarcinoma. We excluded the patient's lumbar spinal stenosis and chemotherapy as the inciting factors in his leg weakness. The EMG/NCV findings were deemed to be secondary to peripheral neuropathy instead of lumbar radiculopathy. The paraneoplastic sensorimotor peripheral neuropathy was validated by the physical exam and EMG/NCV studies. The patient subsequently declined all medical treatment and testing and died soon thereafter. The PNS was not confirmed by antibody detection.

Conclusion

Neurosurgeons and neurologists should be cognizant of PNS that may manifest as sensorimotor peripheral polyneuropathy in patients with prostate cancer. EMG/NCV and antibody detection are beneficial in confirming and treating this exceedingly rare condition.

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