




## Subacute-onset paraneoplastic autonomic neuropathy associated with prostate cancer

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Dear Editors,

Isolated autonomic failure of acute or subacute onset suggests an immune cause, such as autoimmune autonomic ganglionopathy (AAG) and paraneoplastic autonomic neuropathy/ganglionopathy (PAN) [1]. While PAN may present with a limited enteric neuropathy, both disorders may present with diffuse autonomic failure and be clinically indistinguishable. Characteristic features include orthostatic hypotension, constipation and cholinergic failure such as sicca syndrome, urinary retention and impaired pupil responses. The antibodies most commonly associated with PAN might be directed to intracellular (anti-Hu, anti-CV2) or surface antigens (anti-ganglionic nicotinic acetylcholine receptor [anti-gAChR]) [1]. The former are onconeural antibodies strongly associated with underlying malignancy, most frequently small cell lung carcinoma (SCLC), and related to other paraneoplastic neurological syndromes [2, 3]. Anti-gAChR antibodies are identified at high levels (> 1.0 nmol/L) in more than half of patients with AAG and, in a minority of cases (about 15%), are associated with underlying malignancy (SCLC, thymoma or adenocarcinomas) [1, 4].

Here, we report the case of an elderly patient in whom subacute-onset pandysautonomia lead to the diagnosis of metastatic prostate cancer associated with low titer anti-gAChR antibodies.

A 75-year-old-man with a past history of benign prostate hyperplasia presented at the emergency department with acute urinary retention. A urethral catheter was placed,

resulting in drainage of ca. 1000 cc of urine, and the patient was dismissed with a urology appointment scheduled. After 2 days, he had several syncopal episodes while standing during the morning, and was therefore admitted for further investigation. He was found to have orthostatic hypotension, with a blood pressure drop 3 min after standing of 30/20 mmHg (from 130/80 to 100/60 mmHg, heart rate of 70 bpm, unchanged). Moreover, because of rapidly progressive abdominal bloating and constipation, he underwent an abdominal radiography and, subsequently, colonoscopy, which were consistent with acute colonic pseudo-obstruction (ACPO) [Fig. 1]. Abdominal ultrasound also showed bilateral ureteronephrosis. Neurological examination was unremarkable and, specifically, no sensory-motor symptoms or signs were present.

Considering the isolated subacute-onset pandysautonomia of possible paraneoplastic origin, the patient underwent a contrast-enhanced thoracoabdominal CT, which showed a prostatic heteroplasia and several bone metastases at the pelvis and dorsolumbar vertebrae.

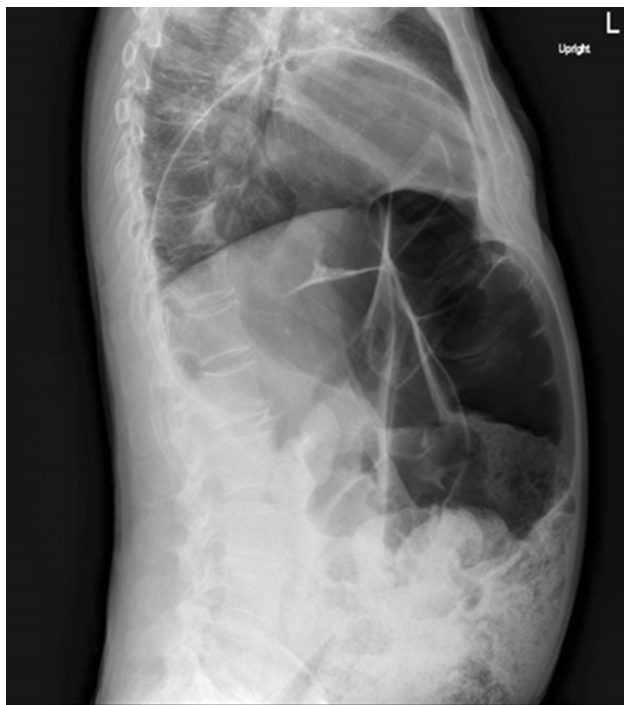
Cerebrospinal fluid (CSF) showed a normal cell count and elevated protein levels (83 mg/dL) and CSF/serum albumin ratio (19.4). A serologic panel of onconeural antibodies inclusive of anti-Hu and anti-CV2 was negative, while anti-gAChR was positive at low titer (0.05 nmol/L). The patient was treated with intravenous steroid pulses (methylprednisolone 1 g/day for 5 days), then tapered to oral prednisone 50 mg/day. This led to prompt resolution of the orthostatic hypotension (blood pressure of 130/80 mmHg, unchanged in supine and standing position), in addition to maintenance of regular bowel movements after colonoscopic decompression. It was not possible to wean off the urinary catheter, possibly as a consequence of the prostate cancer. During hospitalization, he developed severe coronavirus disease 2019 and prednisone was discontinued, leading to relapse of ACPO. The patient was eventually commenced on hormone therapy for prostate cancer and transferred to a long-term care facility.

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**Fig. 1** Abdominal X-ray showing a massive colonic dilatation, consistent with acute colonic pseudo-obstruction

To our knowledge, this is the first report of subacute-onset PAN associated with prostate cancer. The patient at issue developed diffuse autonomic failure involving the sympathetic, parasympathetic and enteric nervous system (causing orthostatic hypotension, acute urinary retention and ACPO, respectively), partially responsive to high-dose steroid therapy. This presentation is clinically indistinguishable from AAG. Screening for occult malignancy by CT revealed a prostatic heteroplasia with bone secondaries, otherwise asymptomatic.

Prostate cancer is the second most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide [5]. It has been rarely reported in association with paraneoplastic neurological syndromes (PNS): in the most recent review on this topic, among 37 reported cases with PNS and prostate cancer, only one patient presented with anti-Hu-associated limited gastrointestinal neuropathy, and no one with pandysautonomia [6].

Anti-gAChR antibodies at intermediate or low titers have been found in three patients with prostate cancer (in two cases with values in the range of 0.10–0.99 nmol/L, in one case with values in the range 0.03–0.09 nmol/L) in a single study describing the frequency of anti-gAChR seropositivity among 15,000 patients evaluated for paraneoplastic antibodies [4]. However, no detailed clinical information is available for these specific subjects.

Our patient was found to have low levels of anti-gAChR antibodies, which have been demonstrated to be quite nonspecific

for pandysautonomia at this titer [1]. Therefore, it is not clear whether these antibodies had a pathogenic role in determining PAN in our patient, or represent an epiphenomenon possibly related to the presence of prostate cancer. This notwithstanding, the marked improvement of autonomic symptoms following steroid therapy suggests that PAN was immune-mediated. In general, treatment of PAN is first directed at eradicating the underlying malignancy, but immunotherapy may also be attempted to control dysautonomic symptoms [1]. While plasma exchange and intravenous immunoglobulin might be beneficial in anti-gAChR-mediated PAN, high-dose corticosteroids might be more effective in PAN forms related to onconeural antibodies.

In conclusion, subacute diffuse autonomic failure should be considered among the spectrum of PNS associated with prostate cancer. As in our patient, PAN may precede the diagnosis of cancer. Therefore, prompt screening for occult malignancies should be performed in adult patients presenting with subacute pandysautonomia, as this may have an impact on cancer prognosis.

**Author contributions** LM drafted the manuscript; LM and MN contributed to the acquisition of data; all authors contributed to the analysis of data; MN, PC and MG critically revised the manuscript for intellectual content.

## Compliance with ethical standards

**Conflict of interest** The authors report no relevant disclosures, conflicts of interest or funding sources for this work.

**Ethical approval** We confirm that approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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