CASE REPORT

Paraneoplastic encephalopathy: an unusual presenting feature of bladder cancer metastasis

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SUMMARY

A 73-year-old woman with a history of localised transitional cell cancer (TCC) of the bladder, resected 22 years prior, presented with tremor, gait unsteadiness and cognitive deficits. Basic neurological workup was negative and CT of the abdomen revealed recurrent TCC with a solitary pelvic metastasis. She was treated with surgical resection of her tumour and immunosuppression. Her symptoms resolved, and it was felt her presentation was consistent with paraneoplastic encephalopathy in the setting of bladder cancer metastasis. She has remained disease and symptom free over 5 years of follow-up. This case report reviews the mechanism, clinical features and treatment of paraneoplastic neurological syndromes, and discusses briefly the management of oligometastatic recurrent bladder cancer.

BACKGROUND

Paraneoplastic neurological syndromes (PNS) are a rare group of immune-mediated disorders associated with an often occult underlying malignancy. They may involve any part of the central and peripheral nervous system, and they have a wide range of presentations including limbic encephalitis, peripheral neuropathy, myasthenic syndrome and any constellation of overlapping clinical syndromes in between. PNS are felt to be a result of antibodies that react both with the underlying cancer and autoantigens of the nervous system.¹ PNS is most commonly observed with small cell lung cancer. Less often, tumours of the breast, gastrointestinal tract, thymus, melanoma and teratoma have been associated with these syndromes.² Transitional cell cancer (TCC) of the bladder is typically not associated with PNS.³ We report a case of recurrent bladder cancer with a solitary pelvic metastasis that presented with symptoms of paraneoplastic encephalopathy 22 years after initial cancer diagnosis, and discuss management.

CASE PRESENTATION

A 73-year-old woman, a former interpreter, with a remote history of radical cystectomy 22 years prior, presented with bilateral hand tremor and mild gait unsteadiness over 2 months. A trial of β blocker for the tremor was unsuccessful. Within 1 month her neurological symptoms progressed. She developed cognitive deficits, including memory loss and word finding difficulty. These resulted in inability to speak in sentences of more than two or three words and failure to perform daily activities of living, such as accessing her email or conducting

financial transactions. She also started experiencing severe involuntary jerky movements, frequent staring spells and episodes of loss of consciousness. The neurological symptoms were accompanied by a 10 lb weight loss and anorexia. The neurological examination was remarkable for myoclonus, hyper-reflexia and intermittent gait ataxia. Initial neuropsychological assessment detected impaired lexical greater than semantic fluency and drawing of complex geometric figures. Later, the patient showed severe short-term memory deficit and disorientation to time and place.

Her medical history included a pG3T1N0M0 TCC of the bladder, for which she had undergone radical cystectomy and ileal conduit diversion 22 years prior. Since that time, periodic urological surveillance was performed, with no evidence of disease recurrence, and she did not have any other health symptoms.

INVESTIGATIONS

Laboratory workup revealed a normal complete blood count, electrolytes, vitamin B₁₂, folate, thyroid-stimulating hormone, liver enzymes, ammonia, creatinine, serum copper and ceruloplasmin, urine heavy metal screen, HIV antibodies and erythrocyte sedimentation rate. C reactive protein was slightly elevated at 8.9 mg/mL (normal <8.0). Antinuclear and SS-A/Ro antibodies (abs) were positive with negative SS-B abs. Cerebrospinal fluid (CSF) analysis was unremarkable. Paraneoplastic antibodies, including antineuronal nuclear antibody (ANNA-1, ANNA-2 and ANNA-3), antiglial nuclear antibody (AGNA-1), Purkinje cell antibody (PCA-1, PCA-2 and PCA-Tr), amphiphysin, collapsin response mediator protein (CRMP-5), striated muscle, P/Q-type (P/Q-VGCC) and N-type calcium channel (L-VGCC), voltage-gated potassium channel antibodies (VGKC), N-methyl-D-aspartate receptor (NMDA-R), γ -aminobutyric acid type B receptor (GABAB-R) and glutamic acid decarboxylase (GAD65) antibodies, were negative in the serum and in the CSF.

EEG showed no epileptogenic activity. A multi-channel surface electromyography recording demonstrated action myoclonus predominantly in the upper limbs. MRI of the brain and cervical spine, with and without contrast, and MR angiography, were unremarkable. Mammogram and CT of the chest, abdomen and pelvis to search for an underlying malignancy revealed a 4.8×4.5 cm mass in the left side of the pelvis, between the external iliac and internal iliac vessels (figure 1).

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Figure 1 CT of the abdomen and pelvis revealing a 4.8×4.5 cm mass in the left side of the pelvis, ultimately proven by biopsy as recurrent transitional cell cancer.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for subacute cognitive decline and associated myoclonus is broad, and includes acquired and inherited metabolic disorders (eg, hepatic encephalopathy), inflammatory diseases (eg, vasculitis), infectious diseases (eg, Creutzfeldt-Jakob disease), autoimmune encephalopathy (eg, anti-NMDA ab-associated encephalopathy), genetic disorders (eg, mitochondrial diseases) and, less commonly, degenerative dementia, psychiatric disorders and paraneoplastic diseases. Biopsy of the left pelvic mass on the patient's CT scan revealed metastatic non-small cell carcinoma suggestive of urothelial origin. Given the clinicopathological correlation and the lack of evidence for other abnormalities that could have accounted for the neurological disorder, despite the absence of canonical paraneoplastic antibodies, it was felt that the patient's encephalopathy and myoclonus represented a paraneoplastic disorder in the setting of recurrent TCC.

TREATMENT

The patient initially received a 5-day course of methylprednisolone (1 g intravenously daily) without significant clinical improvement. After a multidisciplinary consultation between neurology, medical oncology and urology teams was obtained, she underwent abdominal pelvic exploration and metastasectomy of the left pelvic mass. Pathology confirmed metastatic poorly differentiated carcinoma with squamous features largely replacing a pre-existing lymph node and forming a 6.5×4.8×3.7 cm mass. The clinical estimate was that this lesion represented metastasis related to the patient's original tumour 22 years prior. The postoperative course was uncomplicated. Adjuvant chemotherapy was offered but the patient favoured observation. At follow-up 6 weeks after surgery, she demonstrated improvement in her cognitive symptoms. She was able to speak fluently again. However, she did note persistent mild word-finding difficulty, tremor and memory loss. Given persistence of these symptoms 2 months postoperatively, a repeated 5-day course of methylprednisolone was administered, followed by a slow oral prednisone taper over 6 months.

OUTCOME AND FOLLOW-UP

The patient reported progressive resolution of her symptoms after definitive management of her tumour and adjunctive immunosuppression. She had returned to near baseline cognitive status by 5 months after her metastasectomy. At 5 years of follow-up since metastasectomy, with clinical examination,

routine laboratories, and CT of the abdomen and pelvis every 4–6 months, she has had no relapse of her neurological symptoms and no evidence of recurrent bladder cancer.

DISCUSSION

PNS are a heterogeneous group of immune-mediated neurological disorders associated with underlying malignancy. In this case, the patient was thought to have a paraneoplastic encephalopathy arising in the context of recurrent bladder cancer. The pathogenesis of PNS is related to ectopic expression by a tumour of an antigen that is typically restricted to the nervous system. The immune system identifies these onconeural antigens as foreign and mounts a response. The activated antibodies and cytotoxic T cells only cause neurological disease when they cross the blood–brain barrier via poorly understood mechanisms and react with neurons expressing the onconeural antigen.^{4 5} Therefore, the paraneoplastic autoimmunity is essentially driven by cancer-associated onconeural antigens. Diagnosis typically involves evaluation for a single or multiple coexisting onconeural antibodies in the blood and/or CSF.⁶ The antibody itself may be pathogenic against an extracellular antigen or it may be a diagnostic marker of an intracellular onconeural antigen being targeted by a cytotoxic T cell. Such antibodies often coexist in specific clusters, that may suggest the presence of a given neoplasm and the paraneoplastic basis of the neurological syndrome.⁷ However, PNS can occur in the absence of onconeural antibodies and the antibodies can occur in the absence of a neurological syndrome,⁸ challenging the diagnosis. It has been estimated that approximately 18–50% of patients with PNS have no onconeural antibodies, and that seropositive and seronegative patients with PNS share similar features.^{9 10} These findings emphasise the importance of a clinical suspicion for PNS and the relevance of the Graus criteria according to which PNS can be diagnosed in the right clinical setting despite the lack of cancer and onconeural antibodies.⁸ While the underlying tumour may be asymptomatic and indolent, the neurological syndrome is often rapidly progressive, severe and potentially lethal. Our patient had no detectable paraneoplastic antibodies, but the lack of evidence for other aetiologies that could have accounted for the neurological symptoms, and the clinical improvement following resection of the tumour and immunotherapy, support the paraneoplastic aetiology.

Treatment of PNS is twofold, directed at removal of the antigen source via treatment of the underlying tumour, often combined with suppression of the immune response. Immunotherapy may include use of corticosteroids, plasma exchange, intravenous immunoglobulin or steroid-sparing immunosuppressant drugs. For paraneoplastic disorders such as Lambert-Eaton myasthenic syndrome, removal of the cancer and symptomatic treatment with 3,4-diaminopyridine may be sufficient.

Classically associated with small cell lung cancer, PNS has been reported in a variety of other tumour types including thymoma, Hodgkin lymphoma and tumours of the breast, gastrointestinal tract, lung and gynaecological system. PNS is not commonly a manifestation of bladder cancer. Case reports have described peripheral neuropathy, paraneoplastic cerebellar degeneration, opsoclonus-myoclonus-ataxia syndrome and Lambert-Eaton myasthenic syndrome as associated with underlying TCC.³ To the best of our knowledge, this report represents the first case of paraneoplastic encephalopathy attributable to underlying TCC. The second striking and unusual feature of this case is the time frame of the disease relapse. The patient's initially localised, non-muscle invasive, surgically resected

bladder cancer recurred with a metastatic lesion 22 years after diagnosis. Most local recurrences or metastases from bladder cancer after cystectomy occur in the setting of muscle-invasive disease and present within 3 years of diagnosis.¹¹ Metastatic bladder cancer is typically incurable. However, a recent German series described use of surgery for curative intent in metastatic urothelial carcinoma.¹² In the setting of very indolent and oligo-metastatic disease, surgical resection for curative intent is a viable treatment strategy. In this patient, the combination of tumour removal and extended immune suppression led to a durable remission of neurological symptoms as well as extended disease-free survival to date.

Learning points

- ▶ Paraneoplastic neurological syndromes (PNS) are rare immune-mediated disorders that are clinically diverse in presentation.
- ▶ Treatment of PNS is based on definitive management of the underlying tumour and, often, associated immunotherapy.
- ▶ Transitional cell cancer (TCC) of the bladder is rarely associated with PNS and most often presents with symptoms of local invasion, though in this case we reported an unusual occurrence of paraneoplastic encephalopathy as the presenting feature of recurrent TCC.
- ▶ Local recurrence or metastasis from bladder cancer most often arises within 3 years of diagnosis. Late recurrences of non-muscle invasive disease are uncommon.
- ▶ Surgery with curative intent for indolent, oligometastatic TCC can be considered.

Contributors GT wrote and revised the manuscript, reviewed the literature and currently follows the patient who was reported. MK saw the patient at presentation

to oncology, developed the idea for using her case as an opportunity to review this condition and reviewed the manuscript. MM saw the patient on initial presentation to neurology, reviewed the manuscript, and contributed valuable insights and references to the discussion on paraneoplastic neurological syndromes.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Didelot A, Honnorat J. Chapter 78—paraneoplastic disorders of the central and peripheral nervous systems. In: José B, José MF, eds. *Handbook of clinical neurology*. Elsevier, 2014:1159–79.
- 2 McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. *Acta Neuropathol* 2011;122:381–400.
- 3 Sacco E, Pinto F, Sasso F, et al. Paraneoplastic syndromes in patients with urological malignancies. *Urol Int* 2009;83:1–11.
- 4 Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. *Neurology* 2011;77:179–89.
- 5 Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med* 2003;349:1543–54.
- 6 Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol* 2004;56:715–19.
- 7 Horta ES, Lennon VA, Lachance DH, et al. Neural autoantibody clusters aid diagnosis of cancer. *Clin Cancer Res* 2014;20:3862–9.
- 8 Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
- 9 Voltz R. Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis, and therapy. *Lancet Neurol* 2002;1:294–305.
- 10 Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 2010;67:330–5.
- 11 Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466–77.
- 12 Lehmann J, Suttman H, Albers P, et al. Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). *Eur Urol* 2009;55:1293–9.

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