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Case report | Prikaz bolesnika

Neurologic paraneoplastic syndrome in renal cell carcinoma – a diagnosis mislead by the death of a mouse

Paraneoplastički neurološki sindrom uz karcinom bubrega – dijagnostički zavaravajuća smrt miša

Marjan Marić[1], Lorna Stemberger Marić[2,3], Ivan Kurealc[2], Adriana Vince[2,3], Željko Kaštelan[1,3], Neven Papić[2,3]

[1] University Hospital Centre Zagreb, Department of Urology, Zagreb, Croatia
[2] University Hospital for Infectious Diseases „Dr. Fran Mihaljević", Zagreb, Croatia
[3] University of Zagreb, School of Medicine, Croatia

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Summary

Neurologic symptoms secondary to a paraneoplastic syndrome (PNS) may be the presenting manifestation of a previously undiagnosed cancer. This case highlights the potential complexity of the PNS associated with renal cell carcinoma, confusion and delay of diagnosis due to positive mouse bioassay, latter presentation as encephalitic syndrome, positive outcome associated with initial treatment with total plasma exchange, as well as absence of recurrence of neurologic symptoms after complete surgical removal of tumour.

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✉ **Corresponding author:**
Marjan Maric, MD, urology specialist
Department of Urology, University Hospital Centre Zagreb, Croatia
E-mail: marjanmaric1980@gmail.com
ORCID: 0000-0002-5002-3492

Sažetak

Neurološki simptomi mogu predstavljati i paraneoplastički sindrom (PNS) uslijed nedijagnosticiranog tumora. Ovaj prikaz bolesnika ističe potencijalnu složenost PNS-a povezanog s karcinomom bubrega, zabunu i kašnjenje dijagnoze zbog pozitivnog biološkog testa na mišu, kliničku prezentaciju u obliku sindroma encefalitisa, pozitivnog ishoda povezanog s početnim liječenjem plazmaferezom, kao i odsutnost recidiva neuroloških simptoma nakon potpunog kirurškog uklanjanja tumora.

Introduction

Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of immune-mediated central or peripheral nervous system disorders that result from indirect effects of malignant disease. Most patients develop a 'classical' PNS, the most frequent being paraneoplastic cerebellar degeneration (PCD), sensory neuronopathy, and limbic encephalitis. Tumors usually associated with PNS are small-cell lung cancer, thymoma, breast, ovary and testicular cancers or neuroblastoma. Given the diverse and atypical clinical presentation, diagnosing PNS is challenging and often delayed[1, 2].

We describe a case of a 53-year-old male who initially presented with acute encephalitic syndrome which proved to be PNS caused by renal cell carcinoma (RCC), ultimately. We also provide a comprehensive literature review on paraneoplastic neurologic disorders associated with RCC (Table 1). This case highlights the importance of considering seronegative PNS in patients with acute encephalitic syndromes after infectious and metabolic causes have been excluded.

Case report

In October 2019, a previously healthy 53-year-old male patient was admitted due to headache, vertigo and somnolence. Brain MRI and CSF examination were normal. Next day he developed generalized muscular weakness, urinary retention, bilateral ptosis and diplopia (no mydriasis). Although EMNG results were normal, due to suspicion of myasthenic syndrome, pyridostigmine was started and gradual resolution of symptoms followed. Anti–acetylcholine receptor (AChR) antibody (Ab) test for myasthenia gravis (MG) complex came negative, but mouse

Table 1. Literature review of paraneoplastic neurologic disorders associated with renal cell carcinoma
Tablica 1. Pregled literature o paraneoplastičkim neurološkim poremećajima povezanih s karcinomom bubrega

Symptoms/syndrome	Author, year	cases reported, n	gender, age	RCC subtype, d (cm)
Limbic encephalitis	Bell, 1998 Harrison, 2015 Zhu, 2019 Jang, 2021	24 1 1 3	 f, 66y m, 54y f, 54 y m, 51y f, 54y	clear cell sarcomatoid, 8 cm clear cell, 5,5 cm clear cell, 2,2 cm clear cell, 2,5 cm chromophobe, 3,7 cm
Demyelinating neuropathy Lower motor neuropathy	Allen, 2011 Foreman, 1999	1 1	m, 61y f, 70y	papillary, NA granular cell, 2cm
Chronic inflammatory demyelinating polyneuropathy	Nishioka, 2017 Yang, 2017	1 1	m, 50y f, 61y	clear cell, 6,3 cm clear cell, 1,4 cm
Acute demyelinating polyradiculopathy	Roy, 2002	1	m, 65y	clear cell, 6,5 cm
ALS	Turk, 2009 Evans, 1990	1 1	m, 59y m, 74y	clear cell, 9,5 cm
Myasthenia gravis	Torgerson, 1999 Zheng, 2021	1 6 (1)	m, 38y m, 59	clear cell, 3 cm clear cell, 8,5 cm
Myopathy	Solon, 1994 Naert, 2015	1 1	f, 78y m, 49y	NA, 2 cm clear cell, 5 cm
Opsoclonus-myoclonus	De Luca, 2002 Gimeno Campos, 2006 Koukoulis, 1998.	1 1	m, 37y m, 64y 	clear cell, 3,5 cm papillary, NA
Stiff Person syndrome	McHugh, 2007	1	m, 53y	clear cell, NA
Frontal lobe disorder	Hagel, 2005	1	m, 60y	clear cell, NA
Ataxia	Hagel, 2005	1	m, 60y	clear cell, NA
Cerebellar degeneration	Johnson, 2008 Souza, 2019 Ammar, 2008 Hens, 2008	1 1 1 1	m, 53y f, 75y f, 64y m, 66y	clear cell, 10,4 cm clear cell, 1,6 cm clear cell, NA clear cell, NA
Ballismus/chorea	Kuajawa, 2001	1	m, 55y	clear cell, NA
Guillain-Barre syndrome	Zakrocka, 2020 Alimonti, 2003	1 1	m, 47y f, 65y	papillary, 3 cm clear cell, 3,5 cm
Anti-NMDAR encephalitis	Yang, 2020	1	m, 54y	clear cell, 5cm
Parkinson-like	Ali, 2017	1	m, 74y	clear cell, 7,7cm

lethality botulism bioassay was positive, and the diagnosis of atypical botulism was made, although clinical presentation and the course of disease weren't completely compatible with untreated botulism. The patient's condition improved, and he was discharged two weeks later.

In late December, he was readmitted due to acute onset of coma (GCS 3), hypoxemia, hypothermia and hypotension that required intubation and mechanical ventilation. Brain MRI was normal and CSF showed no pleocytosis and mild proteinorachia (980 mg/L). Extensive diagnostic workup was negative- CSF meningitis/encephalitis panel test for the 14 most common pathogens responsible for community acquired meningitis or encephalitis including viruses, bacteria and yeast, anti-HIV, TPHA, including repeated MG tests (pyridostigmine test, AChR Ab), anti-MAG, anti-ganglioside and paraneoplastic antibodies (mGluR1, AMPAR, GABA-R, ANNA 1-3, PCA 1-3, AGNA-1, amphiphysin, CRMP-5, VGKC, LGI-1,

CASPR, NMDA-R, GAD-65, Anti-Hu, anti-Ma2) and tumor markers (CEA, CA 19-9, β-hCG, NSE, CYFRA 21-1, AFP). Due to new, fulminant onset of acute progressive external ophthalmoplegia, ataxia, and impaired conscious level which progressed to coma, as well as exclusion of other possible causes, severe form of probable Bickerstaff brainstem encephalitis (BBE) was suspected, and pulse doses of methylprednisolone and total plasma exchange (TPE) were started. Total of 8 TPE were performed and neurological deficit resolved, except for mild muscle weakness. Abdominal MSCT showed hypovascular expansive process (3.5 cm) in the left kidney and MRI of the kidney confirmed the expansive heterogeneous tumor. Radical nephrectomy was performed and pathohistology confirmed clear cell renal cell carcinoma (ccRCC) with no signs of extrarenal dissemination (Stage T1a). Finally, due to presence of non-classical neurologic syndrome, absent onconeuronal antibodies and presence of the tumor, as well as clinical improvement after cancer therapy, the diagnosis of PNS related to renal cell carcinoma (RCC) was made. In a 2-year follow up there was no recurrence of tumor or neurologic symptomatology.

Discussion

This case illustrates the importance of considering PNS in an unusual, atypical and insidiously progressive neurologic conditions where no clear alternative diagnosis is convincing, especially since delay in diagnosis and treatment can result in rapid progression and potentially irreversible neurological damage.

There are several learning points in this case report. First, our patient initially presented with myasthenic syndrome, but false-positive botulism bioassay associated with clinical improvement following administration of prostigmine caused delay in diagnosis. Presence of headache and somnolence, absence of mydriasis, dry mouth and constipation makes diagnosis of botulism unlikely, especially when exposure history is negative. Importantly, mouse bioassay has many disadvantages, and false positive tests were previously reported in Guillain-Barré and Miller-Fisher syndromes[3, 4].

Next, the PNS mainly precede the tumor diagnosis and neurological symptoms are present before the malignancy becomes clinically overt. There are no particular clinical patterns, imaging and laboratory abnormalities specific for PNS. In addition, PNS usually occur in patients with lung carcinoma, neuroblastoma or thymoma, but other tumors and malignant lymphomas should be considered as well, as shown in this case[1, 5-9].

RCC accounts for up to 2-3% of cancers and are usually detected incidentally. Diverse clinical presentations of PNS were described in limited literature reports, and therefore are not often considered as indicating factor for RCC. Most neurologic PNS present as peripheral nervous system syndromes and myopathies, as shown in Table 1. Reports on central nervous system presentation are limited to anti-NMDAR and other limbic encephalitis, thus we present the first case of PNS associated with RCC which presented as severe form of Bickerstaff-like brainstem encephalitis[2, 9-15]. Both conditions are antibody-mediated diseases treated with pulse dose methylprednisolone and TPE, which lead to temporal clinical response, as seen in our case.

The role of paraneoplastic antibodies in RCC remains unclear and is a topic of ongoing investigation in the current literature. Previous case reports of paraneoplastic neuropathies associated with RCC have also described negative antibody screens preceding RCC diagnosis. Likewise, our patient was seronegative for some common paraneoplastic antibodies (as shown above). The question remains whether these antibody-negative cases are truly immune-mediated or whether these antibodies have simply not been identified (yet). In our case, the clinical improvement followed initiation of treatment with TPE which suggests the potential presence of undefined antibodies. Here we also highlight that failure to identify an antibody marker should not exclude a paraneoplastic process, particularly if persistence of neurologic syndrome free period follows the removal of the tumor.

In conclusion, we have shown the potential complexity of the neurologic PNS associated with RCC, positive outcome associated with initial treatment with TPE, as well as absence of recurrence of neurologic symptoms after complete surgical removal of the tumor.

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