Anti-Hu Antibodies Associated Paraneoplastic Encephalitis due to Primary Renal Cell (RCC) Carcinoma. A Case Report

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Summary. *Objective.* Study objective is to describe a case of anti-Hu seropositive paraneoplastic encephalitis in association with renal cell carcinoma.

Case report. A 65 year old female patient with a history of hyperstension and structural heart disease was admitted to Respublikinė Vilniaus universitetinė ligoninė (RVUL) neurological ward due to language impairment, sudden onset of hyperkinesia following hearing loss in the right ear, lightheadedness, weakness of the right extremities, asymetric ophtalmopathy, and gait disorder. Blood tests confirmed presence of anti-Hu antineuronal antibodies, and a contrast CT revealed a 7×5×4 cm mass in the right kidney with contrast uptake. Histopathology confirmed renal cell carcinoma.

Discussion. Paraneoplastic neurological syndromes are thought to be immune mediated, with a variety of different mechanisms including antibody mediated and T-cell mediated mechanisms among others. Well characterized antibodies are key to early diagnosis and treatment, but there are seronegative cases with both the presence of tumor and neurologic deficit which cannot be explained by any other likely cause. Treatment options include removal of the tumor as the primary cause and immunomodulation therapy. Most of the time, both options are used simultaneously. Treatment of any underlying conditions and comorbidities may improve the outcome of paraneoplastic neurologic syndromes.

Keywords: paraneoplastic encephalitis, renal cell carcinoma, antibodies, anti-Hu.

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INTRODUCTION

Paraneoplastic syndromes are disorders associated with cancer but without direct effects of the tumor or its metastases. Paraneoplastic encephalitis is an indirect effect of pre-existing cancer on the nervous system through immune mediated mechanisms with a vast array of antineuronal antibodies best known of causing the disease (Anti-Hu, Yo, Ri amphiphysin, Tr, CV2, Ta antibodies, etc). Having many forms and manifestations, including peripheral neuropathy, brainstem encephalitis, limbic encephalitis being one of the more common manifestations, cerebellar degeneration or myelopathy, paraneoplastic encephalitis is known to be caused by all sorts of neoplasms following small cell lung carcinoma, ovarian, prostate cancers, ovarian teratomas, Hodgkins lymphomas, etc. We present a case of motor difficulties, gait disorder, neurosensory deafness, and asymmetric ophtalmopathy caused by immunologically confirmed anti-Hu paraneoplastic encephalitis due to primary renal cell carcinoma.

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CASE REPORT

A 65 year old female patient with a history of hyperstension and structural heart disease was admitted to Respublikinė Vilniaus universitetinė ligoninė (RVUL) neurological ward due to language impairment, sudden onset of hyperkinesia following hearing loss in the right ear, lightheadedness, weakness of the right extremities, asymmetric ophtalmopathy, and gait disorder. The symptoms had been progressing for about a year and the patient underwent multiple hospitalisations in 4 different hospitals around the country. All laboratory tests including complete blood count, coagulation profile, C reactive protein, and erythrocyte sidementation rate (Westergren) were within normal range or showed non-specific inflammatory changes. The patient was consulted by an endocrinologist who found elevated thyreotropic (TTH) hormone level 6.20 mIU/L (normal range 0.27–4.20) which suggested Grave's disease. Analysis of the cerebrospinal fluid (CSF) was negative for Lyme's disease and for viral pathogens as well. Multiple instrumental tests to visualize the brain including multiple contrast/non constrast CT scans and MRIs were performed revealing only non-specific changes such as mild, age related atrophy, leukoencephalopathic changes, and a sub clinical cavernoma in the right frontal lobe.

Table. **Anti-Hu seropositive neoplasms in association with a neurologic syndrome**

	Neurological syndrome	**Tumor**
Anti-Hu seropositive	Encephalomyelitis/limbic encephalitis	SCLC, testicular tumour, thymoma, neuroblastoma, prostate carcinoma, breast cancer, Hodgkin's lymphoma
	Cerebellar degeneration	SCLC, ovarian cancer, breast cancer, Hodgkin's lymphoma, thymoma
	Brainstem encephalitis/ opsoclonus-myoclonus	Breast cancer, ovarian cancer, testicular tumor, SCLC, neuroblastoma (children)
	Subacute sensory neuronopathy	SCLC, breast cancer, ovarian cancer

Upon hospitalization, the physical examination revealed impaired language with episodes of pseudobulbar affect, ptosis of the left eyelid, and protrusion of the left eye. Mydriasis was present in both eyes, nonresponsive to light. Generalised hypotonia and hyperkinesia of the right arm, as well as ataxia of the right arm and both legs were present.

A panel for Antineuronal Nuclear antibodies (ANNA) found strongly positive anti-Hu antineuronal antibodies.

A contrast CT of the abdomen and pelvis was performed and revealed a mass in the right kidney, with signs of contrast uptake suggesting a malignant neoplasm. The tumor 7×5×4 cm in diameter was resected, and a histopathological report confirmed a renocellular carcinoma. Afterwards, the patient was consulted by an oncologist and evaluated for distant metastases (MTS's); no further treatment was indicated.

After the patient underwent a right nephrectomy, her condition became stable, but there was still a neurological deficit present.

A few months after discharge, the patient returned to the RVUL emergency room with worsening ataxia, speech difficulties, gait disorder, ophtalmoparesis, and tetraparesis of the limbs with generalized hypotonia of the muscles. All tests, including CBC, coagulation profile, and CRP were within normal parameters. CT scan of the brain ruled out any acute vascular causes, a chest x-ray and a transabdominal echo ruled out possible relapse of RCC. A urine analysis was performed, suggesting a lower urinary tract infection, later to be confirmed by bacteriology reports, suggesting E.coli infection. The TTH level was reevaluated showing increased levels of TTH – an episode of hyperthyroidism.

After a course of antibiotics for the urinary tract infection and correction of thyroid function, and achieving euthyrosis once again, the patient exhibited dramatically improved neurological condition, with better overall muscle strength and improved ataxia as well. The patient started immunomodulation therapy with oral prednisone 60 mg/day and was discharged afterwards.

DISCUSSION

Paraneoplastic neurological syndromes are rare manifestations occurring in less than 1% of patients with malignancies [1]. Most paraneoplastic syndromes present symptoms, because the tumor secretes hormone like substances which affect metabolic processes in the body. Neurological paraneoplastic syndromes are thought to be immune mediated by a variety of different mechanisms, including antibody mediated per se Lambert Eaton myasthenic syndrome, when antibodies are formed against P/Q- type voltage gated calcium channels (VGCC), T-cell mediated mechanisms confirmed post mortem via brain biopsy showing extensive infiltration of $CD4^+$ and $CD8^+$ T-cells in clinically symptomatic areas of the brain, strongly correlating with retrospectively seropositive anti-Hu, anti-Ri, anti-Ma, anti-Ta patients [2].

Our patient presented as seropositive for anti-Hu antibodies, which are classified as well characterized, because they have a well distinct antigen and can be detected via commercial assays [3]. Seropositive cases comprise the majority of paraneoplastic neurological syndromes and are crucial for a diagnostician to make an early diagnosis. Tumor antigens, which mount an immunologic response and antibody formation, have been identified and assigned to specific neoplasms. Table represents the association between anti-Hu antibody formation in response to a specific neoplasm [4].

In contrast, renal cell carcinomas (RCC's) are not historically known to cause paraneoplastic neurologic syndromes. Only few cases identified paraneoplastic neurological syndromes in association with RCC with a vast array of clinical presentations including neuropsychiatric symptoms too [5, 6]. Well characterized antibodies due to RCC include anti-GAD in some cases of cerebellar degeneration and limbic encephalitis [7]. There have been cases reported, where no particular antibodies against RCC where found, but in the presence of both a malignant neoplasm and new onset of neurologic deficit it has been proposed that some not well characterized antibodies may have formed as well. The fact was demonstrated by using biotinylated serums on fixed human brain specimens [3].

Treatment options are reduced to only a few in cases of paraneoplastic neurologic syndromes. Tumor antigen associated cases can only be treated by removing the pre-existing neoplasm [8]. T-cell mediated disease may be manageable with immunomodulation: in cases of cerebellar degeneration with anti-Yo antibodies or encephalomyelitis with anti-Hu antibodies, tacrolimus or mycophenolate mofetil may be used [9], but no treatment guidelines have been established thus far.

Our patient presented with a worsening condition even after removing the antigen source. This may suggest that the mechanisms involved in the disease progression may have both a humoral and a cell mediated factor. In this particular case, disruption of overall homeostasis, such as a local inflammatory process, may have triggered a systemic immune response, worsening the pre-existing condition. Moreover, the patient was diagnosed with Grave's disease, which by itself may cause both focal neurologic and neuropsychiatric symptoms [10]. Achieving euthyrosis and taking control of a local inflammatory process helped to reduce the burden of the paraneoplastic syndrome. This might suggest that a pre-existing autoimmune condition might have a negative effect on other organ systems via T-cell mediated mechanisms and should be further investigated.

KEY POINTS

- In cases of paraneoplastic neurologic syndromes, malignant kidney diseases should be taken into consideration;
- Anti-Hu antibodies can be associated with renal cell carcinoma;
- Negative antibody tests should not exclude the diagnosis;
- Because both humoral and cell mediated mechanisms have affect on the disease, treatment of the condition should tackle both mechanisms;
- Overall homeostasis should be achieved and maintained in order to achieve the best possible outcome for the patient.

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ANTI-HU ANTIKŪNŲ, ASOCIJUOTŲ SU RENOCELIULINE KARCINOMA, SUKELTAS PARANEOPLASTINIS ENCEFALITAS

Santrauka

Tikslas. Aprašyti atvejį, kai paraneoplastinį encefalitą sukėlė anti-Hu antikūnai, produkuojami prieš pirminę renoceliulinę karcinomą.

Atvejo aprašymas. 65 m. pacientė paguldyta į Respublikinės Vilniaus universitetinės ligoninės Neurologijos skyrių dėl kalbos sutrikimų, atsiradusių rankų hiperkinezių, smegenėlinės ataksijos, klausos sutrikimo dešiniąja ausimi, galvos svaigimo. Imunologiniais tyrimais patvirtinti stipriai teigiami anti-Hu antikūnai, o pilvo organų KT metu rastas 7 × 5 × 4 cm darinys dešiniajame inkste, kaupiantis kontrastą. Histologiškai nustatyta renoceliulinė karcinoma.

Aptarimas. Paraneoplastiniai encefalitai, kaip manoma, yra imuninės kilmės, o patogenezinėms ligos grandims galima priskirti tiek ląstelinius, tiek humoralinius imuninės sistemos faktorius. Imunologiniais tyrimais aptikti antineuroniniai antikūnai padeda diferencijuoti susirgimą nuo kitų ligų, tačiau pasitaiko ir atvejų, kai neįmanoma imunologiškai aptikti ligą. Patvirtintų gairių ar rekomendacijų ligai gydyti nėra, o pats gydymas apsiriboja etiologinio veiksnio šalinimu ar imunomoduliacine terapija. Gretutinių ligų gydymas, ypač autoimuninių, gali pagerinti bendras išeitis ir šių pacientų gyvenimo kokybę.

Raktažodžiai: renoceliulinė karcinoma, paraneoplastinis encefalitas, anti-Hu antikūnai.

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