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*CASE STUDY*

# PARANEOPLASTIC LIMBIC ENCEPHALITIS – A CASE REPORT

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## ABSTRACT

**Introduction.** Paraneoplastic neurological syndromes (PNS) refer to a diverse group of nervous system disorders associated with tumors. They are not directly caused by a tumor's immediate expansion, compression resulting from it, infiltration or anti-cancer treatment. Their pathomechanism involves damage to the nervous system as a result of the organism's immune response directed against cancer antigens, and also against antigens occurring physiologically in the nervous system. Onconeural antibodies and cytotoxic T lymphocytes are responsible for the immune response. These conditions are quite rare – fewer than 1 person out of 100 patients suffering from cancer develops PNS. They often precede a direct manifestation of cancer. The best known PNS conditions include: Lambert–Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration, and polyneuropathies. PNS was identified for the first time in 1949. Nowadays, the criteria established in 2004 by Graus et al. have been followed in diagnostics. These define the conditions for arriving at a possible and definite diagnosis based on the presence of a characteristic neurological syndrome, the presence of onconeural antibodies, and detecting neoplasm before or after the manifestation of neurological symptoms. Diagnosis is difficult due to the lack of laboratory markers (onconeural antibodies are present in serum only in 50–60% of cases) or direct cancer symptoms in the first phase of the disease.

**Aim.** This paper aimed at recounting the existence of a very rare neurological syndrome, limbic encephalitis, which can develop in the course of a neoplastic disease. Awareness of PNS and detecting neoplasm before its direct clinical manifestation can contribute to a better prognosis for patients.

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**Materials and methods.** This paper is based on a case analysis concerning a patient manifesting symptoms of the limbic system involvement. The medical history has been interpreted, additional examination results have been analyzed, and the developing clinical manifestations have been investigated.
**Case study.** The presented patient is a 45-year old man in whose case limbic encephalitis exceeded detecting abdominal cancer by a year. Diagnostic difficulties were caused by a synchronous pituitary microadenoma and hormonal disturbances involving cortisol and prolactin, which suggested Cushing's syndrome. The main clinical symptoms, intensifying in time during the course of the disease lasting several months included: recent memory disturbances, allopsychic disorientation, depression, and periodical aggression.
**Results and discussion.** Conducted serum tests to screen for onconeural antibodies did not confirm their presence. However, a magnetic resonance imaginig (MRI) scan revealed bilateral hippocampal damage. On the basis of a typical clinical syndrome, and cancer identified after a year following the occurrence of the symptoms, a definite, according to Graus' criterion, diagnosis of PNS was established.
**Conclusions.** Awareness and knowledge of PNS contributes to an early diagnosis and detection of cancer. This creates an opportunity to introduce adequate treatment and improves the prognosis for the patient.

**Key words:** paraneoplastic neurological syndrome (PNS), paraneoplastic limbic encephalitis (PLE), abdominal cancer

## INTRODUCTION

The term "paraneoplastic" was first used by Guichard who analyzed cases of patients who manifested features of nervous system involvement, yet their autopsies did not detect metastases to the brain or spinal cord [10]. Reports of similar cases had appeared much earlier, and the first known publication concerning this problem dates back to 1890. Auché [2] described a patient with a neoplasm who manifested symptoms of polyneuropathy.

Pathophysiology of paraneoplastic neurological syndrome (PNS) involves immune system response to the presence of oncogenes, proteins in the tumor cells. Physiologically identical or similar proteins are also present in the nervous system, yet thanks to the blood-brain barrier, they are inaccessible for the cells of the immune system. When a neoplasm develops, due to the circulating cytokines this barrier becomes less tight for onconeural antibodies and cytotoxic T (Tc) lymphocytes circulating in the serum. It is believed at present that Tc lymphocytes are primarily responsible for nervous tissue damage. This is confirmed, among others, by a lack of onconeural antibodies in a majority of syndromes [12].

PNS is a rare clinical condition associated with a neoplastic disease, co-occurring with the neoplasm in less than 1% of cases [17]. Some neoplasms, however, more often induce neurological symptoms than others. These include: small cell lung cancer, thyroid cancer, ovarian cancer, and breast cancer; the incidence of PNS in the course of such cancers is estimated to range from 10–15% [4, 13, 15, 18, 21]. Neurological syndromes frequently precede direct manifestation of the neoplasm itself, since a small amount of neoplastic tissue is sufficient to induce an immune response.

In 2004, Graus et al. established the criteria for recognizing PNS [9]. These experts divided PNS into typical, consisting of: encephalitis, myelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus syndrome, subacute sensory neuropathy, chronic intestinal pseudo-obstruction, Lambert–Eaton myasthenic syndrome, dermatomyositis and other, untypical ones, such as: paraneoplastic retinopathy, subacute necrotizing myopathy, motor neuron syndrome, demyelinating neuropathies, neuropathies with axonal loss, neuromyotonia, and polymyositis. A panel of the so-called well-characterized onconeural antibodies (of the highest specificity) was established. The following antibodies were included in it: anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, and anti-amphiphysin. PNS diagnosis is definite if one of the following situations occurs:

- neurological syndrome typical of PNS (classical) and neoplasm recognized within 5 years,
- untypical neurological syndrome, which regresses or improves after neoplasm treatment without concurrent immunotherapy, spontaneous remission of the tumor being excluded,
- untypical neurological syndrome with determining (or without) the presence of onconeural antibodies and diagnosing neoplasm within 5 years,
- neurological syndrome (typical or untypical) with well characterized onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, and anti-amphiphysin), but without the presence of neoplasm.

If a definite diagnosis cannot be established, but a typical neurological syndrome without the presence of the neoplastic process and onconeural antibodies, but with a high-risk of developing neoplasm is observed, or a neurological syndrome (typical or untypical) with only partially characterized onconeural antibodies and no neoplasm is detected, a diagnosis called possible is established. Such a diagnosis may be also established retrospectively, if an untypical neurological syndrome without antibodies is observed and the neoplasm is detected within 2 years.

The term "limbic encephalitis" was first used by Corsellis in 1968 [3]. This condition is rare. It is estimated that it develops in only 1 person out of 10 thousand patients with neoplasm [5]. The limbic system – the term introduced by Brock – is a set of structures that lies around the diencephalons, creating a ring (*limbus*) that

includes: the hippocampus, amygdala, perirhinal cortex, fornix, mammillary bodies, thalamus, and hypothalamus. It is responsible for the creation of emotions and for interpreting external and internal stimuli [8]. A clinical picture of paraneoplastic limbic encephalitis (PLE) is dominated by behaviors stemming from increasing mood and personality disturbances. A quick progression of dementia and the occurrence of delirium are observed, depression develops and epileptic seizures appear [11, 19, 20]. Diagnosis is usually difficult because similar symptoms can be manifested as a result of the development of a neoplasm and also in the course of other diseases – toxic and metabolic encephalopathies, viral encephalitis, Hashimoto's encephalopathy [6]. Diagnosis is also difficult due to a lack of laboratory markers concerning this disease, whereas symptoms usually precede the appearance of neoplasm. Initially, computed tomography (CT) and magnetic resonance imaging (MRI) usually show normal structures [16]. Pleocytosis may be evident in the cerebrospinal fluid [19]. The electroencephalogram (EEG) result is neither typical nor pathognomonic. In some patients EEG result is normal even when epileptic seizures occur. Slowing down the basic rhythm or slow wave clusters have been described both in patients with clinical epileptic seizures (also during inter-seizure periods), and without such seizures [7]. The frequency of occurrence of onconeural antibodies in patients with PLE has not been examined [11]. In many patients it is not possible to detect them. At present, the sensitivity of testing for onconeural antibodies in determining paraneoplastic etiology of a neurological syndrome is estimated to be 50–60% [14, 22].

## AIM

This paper aims at recounting the existence of a very rare neurological syndrome, limbic encephalitis, which can develop in the course of a neoplastic disease. Awareness of PNS and detecting neoplasm before its direct clinical manifestation can contribute to a better prognosis for patients.

## MATERIALS AND METHODS

This paper is based on a case analysis concerning a patient manifesting symptoms of the limbic system involvement. The medical history has been interpreted, additional examination results have been analyzed and the developing clinical manifestations have been investigated.

## CASE STUDY

The patient, A.K., 45-years old, higher education, employed previously as a tourist guide, unemployed preceding becoming ill (he resigned from his job a few months earlier because of a growing feeling of tiredness and lowered mood lasting half a year), was admitted in June 2009 to an Emergency Department due to a sudden loss of consciousness which happened for the first time in his life, associated with

generalized convulsions, as observed by witnesses. Laboratory tests detected glicemia within a range of 400 mg%, thus the patient was hospitalized at the Department of Diabetology with a preliminary diagnosis of a newly discovered diabetes with a symptomatic epileptic seizure. During the following diagnostic procedures, elevated levels of adrenocorticotropic hormone (ACTH) and cortisol were discovered. An MRI scan revealed pituitary microadenoma. A CT of the chest and abdominal cavity did not detect abnormalities apart from features of liver steatosis. Because of evident dejection, the patient was consulted by a psychologist. He was discharged with a diagnosis of pituitary microadenoma and suspicion of Cushing's syndrome, severe obesity, diabetes, arterial hypertension, epileptic disorders to further diagnostics, and suspicion of masked depression. Despite the ordered treatment, the patient complained of poor well-being, progressing general weakness, and lowered mood. Due to those complaints, he was admitted after a few weeks to the Clinic of Endocrinology. Because the hormonal markers assayed again were normal, a definite diagnosis of Cushing's syndrome was not established. The patient was advised to take antidepressants and report for a follow up visit after 3 months. In August 2009, the patient reported episodes of sudden stupefaction, preceded by olfactory sensations occurring every few days and loss of contact, without falling down. Due to these symptoms, he was hospitalized in the Department of Neurology. An EEG detected seizure-related lesions, especially prominent in the temples, and a slightly slower bioelectric activity. A temporal lobe epilepsy was diagnosed. Antiepileptic treatment was introduced, initially with carbamazepine, and next, because of its poor tolerance, levetiracetam, resulting in a regression of seizures. After a few weeks of staying at home, his wife noticed gradually increasing symptoms involving disorientation with regards to time and place, associated with a growing helplessness, and periodic aggressive attacks directed at family members. Because of these symptoms, in November 2009, the patient was admitted to the Department of Psychosomatics. During hospitalization, the symptoms exacerbated. The patient was transferred to the Clinic of Psychiatry, where MRI spectroscopy was performed. This examination showed bilateral hippocampal damage. This resulted in diagnosing mesial temporal sclerosis. During hospitalization one generalized tonic-clonic seizure was observed. However, other cases of loss of consciousness were not excluded. The patient was transferred to the Clinic of Neurology for purposes of further diagnostics and determining antiepileptic medication dosage. During neurological examination performed on the day of admittance, recent and remote memory disturbances and low mood were noted. Video EEG was performed which showed bilateral lesions in frontal, central, and temporal areas, visible as slow sharp wave clusters. In the obtained cerebrospinal fluid a mild cytosis was detected and a slightly elevated level of protein; the levels of anti-*Borrelia burgdorferi* antibodies were normal. Tumor markers CA125, CA15-3, CA 19-9, CEA, and PSA in blood were also normal. A USG scan of abdominal cav-

ity did not show abnormalities. Epileptic seizures were not observed; the previously administered treatment was continued. Since then, the patient stayed at home looked after by his family. He periodically reported to the Outpatient Clinic of Neurology for control examinations. He also continued antiepileptic treatment. In April 2010, blood tests revealed a high level of prolactin (PRL). The patient was consulted by a neurosurgeon who ordered Parlodel. After the administered therapy the level of PRL normalized. However, an increase in the cortisol level was detected. Hence, a CT of the abdominal cavity was performed which showed a large tumor located intra-abdominally and in the hypogastrium, of undetectable origin, with metastases to the liver and lymph nodes. The patient was hospitalized in the Department of Neurology for further diagnostic purposes. The physical examination did not detect focal symptoms involving the central nervous system. A significant exacerbation of psychiatric symptoms was observed, associated with recent memory disturbances, alternate apathy and anger attacks, touchiness, lack of interest in the family, indifference to other people and events. Epileptic seizures were not observed. Blood was obtained to screen for onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, and anti-amphiphysin), and their presence was not detected. A pelvic CT scan, chest X-ray and testicular USG were performed. None of them detected abnormalities. An MRI of the head did not show metastases; an EEG showed changes in the posterior pole of the brain, typical of damage, and epileptic changes in the right temporal lobe. The patient was consulted by a surgeon. A percutaneous biopsy was carried out, which confirmed a neoplastic process, without specifying its origin. The levels of cortisol and PRL were normal. On the basis of the medical history and physical examination, as well the results of additional examinations, limbic encephalitis was diagnosed. Three weeks later, the patient died due to cancerous cachexia.

## RESULTS AND DISCUSSION

In the case described herein, epileptic seizure was the first detected symptom. Medical history indicates earlier emotional disturbances – job quitting, complaints of low mood. Seizures rarely precede other neurological symptoms, yet they can appear within 3 years before detecting the tumor [7]. The clinical picture was further complicated by the suspicions of Cushing's syndrome due to the detected pituitary microadenoma. Analyzing this case retrospectively, the authors believe that disturbances in the cortisol levels were symptomatic of PNS [17]. The leading clinical manifestations during the entire clinical course of the disease involved behavior and psychic disturbances. Imaging scans revealed mesial temporal sclerosis (hippocampus). Such lesions, unilateral or bilateral, have been reported in the course of PLE in some patients [1].

However, it was the detection of an infiltrating abdominal tumor, with suspicions of metastases to the lymph nodes and liver, which allowed for a connecting of all

previous neurological symptoms and the diagnosis of PLE. In the blood, the presence of antineuronal antibodies was not detected – tests were targeted at detecting anti-Ri, anti-Hu, anti-Yo, anti-amphiphysin, anti-CV2.1, and anti-PNMA2/Ta antibodies – although all of them can appear in this disease entity [7]. The lack of these antibodies does not undermine the diagnosis, however, since the clinical picture and the medical history meet Graus' criteria.

The following features support our diagnosis:

- quickly progressing loss of memory, epileptic seizures, psychic degradation indicating the limbic system involvement,
- meeting Graus' criteria – typical neurological syndrome preceded the appearance of the neoplasm by a year,
- excluding other reasons: metastases, infection, encephalopathy, original endocrinological disorders.

## CONCLUSIONS

Early diagnosis of PNS allows physicians to introduce targeted and precise diagnostics, frequently leading to detecting neoplasm in its early stages. This creates an opportunity for beginning treatment and increases the likelihood of surviving. Awareness and knowledge of PNS and their varieties can contribute significantly to a better prognosis for patients.

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