

# Paraneoplastic neurological syndrome in the course of breast cancer

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## ABSTRACT

Paraneoplastic neurological syndromes (PNS) are a group of rarely observed disorders, accompanying about 1% of cancer diseases. They have a typically aggressive course, leading to profound and essentially irreversible disability. The pathogenic cause behind PNS is damage of the nervous system structures as a consequence of the body's immunological reaction induced by cancer. Onconeural antibodies generated as part of the reaction target the tumour tissues, but also the regular nervous tissue recognized as antigens. Presence of onconeural antibodies reveals a 50–60% sensitivity and 100% specificity in diagnosing PNS. Imaging and laboratory tests have a limited impact on diagnosis. What is crucial is the analysis of clinical systems following Graus's criteria (elaborated in 2004). In the case presented here, the patient underwent treatment in many neurological departments due to the symptoms of progressive damage of the nervous system. She was eventually diagnosed with the stiff person syndrome related to breast cancer. In spite of the treatment, including an efficacious oncological therapy, the severe neurological deficit resulted in serious motor disability.

**KEY WORDS:** paraneoplastic neurological syndromes, breast cancer, stiff person syndrome

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## INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are a group of rare disorders, associated with ca. 1% of cancers [8]. They have a typically aggressive course, leading to profound and essentially irreversible disability. Based on the current body of knowledge, the cause behind PNS is damage of the nervous system structures, resulting from the immunological reaction induced by cancer. As a result of the body's humoral response, onconeural antibodies are generated, targeting both the tumour as well as the healthy elements of nervous tissue recognized as antigens. As a consequence of cellular reaction triggered by cytokines, the blood-brain barrier is reduced, and the nervous system is penetrated by immunocompetent cells. Presence of antineural antibodies reveals a 50–60% sensitivity and 100% specificity in diagnosing paraneoplastic neurological syndromes. In around one third of PNS patients, however, their presence is not revealed, and in one fifth of the patients, no neoplasm is observed despite the diagnosis of PNS with antibodies present [1, 5]. Imaging and laboratory tests are of limited use in the diagnostics of PNS, with the diagnosis chiefly based on clinical symptoms assessed in accordance with the 2004 Graus's criteria [1, 4, 6, 7]. In the course of breast cancer, the most frequently observed syndromes include the subacute cerebellar degeneration, stiff person syndrome, opsoclonus-myoclonus syndrome, paraneoplastic retinopathy, and acute necrotizing myopathy [3, 9].

## CASE PRESENTATION

Patient JP-S, aged 43, was admitted to the Neurology Clinic in November 2008 due to muscle weakness and lower limb paraesthesia which had been progressing for 2 weeks. Upon admission, the physical examination reported Lovett grade 3–4 muscle strength as well as abnormal peripheral pain sensitivity, with no symptoms of CNS damage. Additional tests performed reported elevated CRP (113.5 mg/dl), protein in the cerebrospinal fluid (183 mg/dl), pleocytosis 17/3 (100% of mononuclear cells) and IgM anti-bodies against Lyme disease. The EMG test performed upon admission demonstrated bilaterally inhibited conduction in the sural nerve sensory fibres. Head MRI revealed individual periventricular hyperintensities, while cervical spine MRI revealed the loss of physiological lordosis, with slight protrusion of the C4–C5 intervertebral discs, with some dural sac compression. Antibiotic and antiviral therapy was administered in the course of hospitalization. The patient was discharged from the clinic, after her neurological symptoms had been alleviated, and follow-up EMG had revealed improvements of the conduction parameters. Due to the elevated titre of IgM antibodies in the cerebrospinal fluid, neuroborreliosis

had initially been diagnosed, and the patient was referred for further diagnostics to be carried out at the Probationary and Infectious Diseases Department, where the diagnosis was not confirmed.

In January 2009, a right breast nodule was detected, with ultrasound examination revealing features of mild dysplasia and cystic lesions in both breasts.

In February 2009, the patient was readmitted to hospital due to the progression of neurological symptoms, including gait disturbances, upper and lower limb paraesthesia, and increased nuchal muscle tone. During her stay at the Neurology Clinic, the EMG test revealed nerve damage at the level of sensory fibre trunks (loss of active sensory fibres), and axonal sensory polyneuropathy was diagnosed. The EEG test revealed no pathologies, and serum tumour marker results were negative (AFP, CEA, Ca 19.9, NSE, CYFRA 21-1, beta-HCG). Additionally, the patient received psychological and psychiatric consultation, which led to the diagnosis of organic CNS damage in the form of partial cognitive and executive functional deficits as well as depressive/anxiety disorders. The ultimate aetiology of the neurological abnormalities was not determined. The patient was discharged from hospital with persisting neurological symptoms, including gait instability, increased nuchal and cervical muscle tone, extrapyramidal increased limb muscle tone, lack of deep reflexes from upper and lower extremities, superficial sensory abnormalities in distal extremities. The diagnosis was determined as axonal sensory polyneuropathy; extrapyramidal syndrome to be followed up on.

In March 2009, the patient was urgently readmitted to the Neurology Department due to painful cramps, rhythmical spasms of the left upper limb with adduction and maximal flexion in the cubital joint, and posture and gait abnormalities. Neurological examination revealed significant rigidity of spinal axial muscles, intense deep reflexes with remarkable asymmetry ( $L > R$ ) as well as the presence of pathological reflexes ( $L > R$ ). Head CT and EEG did not reveal any deviations from norm. The EMG test, on the other hand, revealed no bioelectrical silence in the trapezius muscle, and features of axonal sensory polyneuropathy in the conduction test. Symptomatic treatment was administered, involving myorelaxants and valproic acid, which resulted in an almost complete regression of the painful spasms of the left upper limb, its improved function, and lower shoulder girdle tone. Physiological hyporeflexia, in particular in lower limbs, was accounted for with the myorelaxing effect of the drugs administered.

While in hospital, the patient received oncological consultation, as a result of which the possibility of a paraneoplastic syndrome was suggested, indicating the necessity to diagnose the right breast lump.

The patient was discharged from the hospital department with the following diagnosis: *Suspected systemic rigidity syndrome (in the course of a paraneoplastic syndrome – mammary gland?)*. The patient was then referred for further diagnostics at the Neurology Clinic. During hospitalisation, her neurological condition deteriorated, with consciousness disturbances, systemic myoclonus, increased nuchal and left shoulder muscle tone, and elevated body temperature reaching 38.5°C. The cerebrospinal fluid analysis was performed, as were EEG and head MRI examinations, revealing no deviations from norm. No metabolically active proliferative disease was revealed under the PET-SPECT examination. The patient was tested for anti-GAD antibodies (negative result), and had tumour marker tests repeated, reporting negative results (AFP, CEA, Ca 19.9, NSE, CYFRA 21-1,  $\beta$ -HCG). At the same time, fine needle aspiration biopsy of the right breast tumour was performed. Its cytologic evaluation reported groups and clusters of cells with no distinct malignancy signs, with numerous lymphoid cells in the background. The microscopic image was determined ambiguous, and it was recommended that the lesion be surgically removed in order to perform a histopathology test. However, the surgery was postponed due to the persisting neurological symptoms. The patient was discharged from hospital with the following diagnosis: *Systemic rigidity syndrome. Sensory polyneuropathy*. Further rehabilitation therapy was recommended, and a follow-up visit at the Neurology Clinic was scheduled a month later.

The rehabilitation therapy carried out in July 2009 brought in clinical improvement.

In September 2009, the patient was yet again hospitalized at the Neurology Clinic. The physical examination reported the pyramidal-extrapyramidal syndrome with left lateralization. Head MRI revealed no pathological lesions, and cervical spine MRI revealed a centrally bulging intervertebral disc at the C3/C4 level, slightly restricting the cerebrospinal fluid reserve volume, with no signs of disc herniation, and no focal lesions within the spinal medulla. Lab test results revealed no abnormalities. The patient was discharged from hospital with the following diagnosis: *Status post encephalitis. Myoclonus epilepsy. C3/C4 discopathy*.

On 22 January 2010, right breast tumorectomy was performed. The resulting histopathology analysis revealed as follows: carcinoma ductale infiltrans NG2G3, mitotic count 20/10 HPF, Ki-67 up to 80%, ER(+++), PR(+++), HER(-), luminal B type. The tumour demonstrated neuroendocrine differentiation, confirmed by the chromogranin A test (6.4 nmol/l, with normal range of 0–6 nmol/l). On 26 February 2010, the right axillary lymph node was biopsied for examination, revealing the presence of cancer cells. The right breast cancer was ultimately staged as T1N1M0, with tamoxifen treatment recommended, and radical Patey's mastectomy, followed by adjunctive chemotherapy, hormonal therapy and radiotherapy.

On 17 March 2010, right breast mastectomy was performed with right-side lymph node dissection. The post-operative histopathology findings included an intramammary lymph node with breast cancer metastasis as well as metastatic lesions in 5 out of the 14 examined right axillary lymph nodes. The patient was post-operatively staged as pT1N2.

In April 2010, the patient initiated adjunctive treatment, involving 3 FAC cycles, followed by 2 docetaxel-based cycles (due to the suspected progression of polyneuropathy, the treatment was discontinued after 2 cycles, with FAC cycle administered instead as the last one). Afterwards, the patient was referred to the Radiotherapy Department. In the period of September through October 2010, she was irradiated with 6MV photons applied to the thoracic cage walls, right-side axillary lymphatic system and supraclavicular region with margin, using conventionally fractionated scheme of df 2 Gy to total dose of 50 Gy. Upon completion of chemotherapy, tamoxifen was administered dosed at 20 mg daily.

In the August of 2011, at the Department of Neurosurgery and Neuropathology of the Neurology Clinic, the presence of anti-amphiphysin antibodies (with the +++ strongly positive result) was demonstrated with the use of indirect immunofluorescence and Western-Blot analysis.

In April 2012, the patient's neurological condition deteriorated. There were painful episodes of paraesthesia, and hyperaesthesia involving both lower extremities. In May 2012, the patient was hospitalized at the Department of Anaesthesiology and Intensive Care, where attempts were made to treat her with plasmapheresis, but no neurological improvement was accomplished. The patient was discharged from hospital with persisting lower limb paraparesis (Lovett's grade 3), "knee highs" sensory disturbances, lack of stretch reflexes, and nystagmus.

Presently, the patient is under systematic follow-up at the Out-patient Oncology Clinic, and continues with the adjunctive tamoxifen treatment. To date, no signs of neoplastic disease progression have been reported. The patient's neurological condition is stable, but has not improved.

## DISCUSSION

Paraneoplastic neurological syndromes (PNS) form a group of neurological disorders involving central nervous system damage in the course of a neoplastic disease. The damage, however, does not result from the tumour's local activity, presence of metastases, treatment toxicity, vascular abnormalities or metabolic deficits [1, 9]. A generally accepted theory explicating the aetiology of PNS is the immunology hypothesis [1, 6–9]. It assumes that the immune system is stimulated by the neoplasm, triggering cellular and humoral response. Humoral response involves the generation of onconeural antibodies targeting both the tumour tissues as well as the normal elements of the nervous tissue recognized as antigens, located in cellular cytoplasm (e.g. within the cytoplasm of the Purkinje cerebellar cells, and of the posterior medullary horns), on cell surface (e.g. voltage-gated potassium channels, calcium channels) or within neuromuscular junctions. As a result of cellular response, mediated by cytokines, the blood-brain barrier is inhibited, and the nervous system is penetrated by immunocompetent cells. In 2002, an international panel of neurologist established a division of antineuronal antibodies into the “well characterised” and “poorly characterised” ones. With reference to the diagnosis of a paraneoplastic syndrome, confirmation of the presence of antineuronal antibodies has ca. 50–60% sensitivity and 100% specificity, but in around 1/3 of patients with diagnosed PNS the presence of antibodies is not reported, and in around 1/5 of patients who are diagnosed with PNS, and who have onconeural antibodies, cancer is not detected [1, 5].

Imaging and lab tests are of limited significance in the diagnostics of PNS. The diagnosis is based on clinical symptoms, taking into consideration the 2004 Graus's diagnostic criteria [1, 4, 6, 7].

Definite PNS has to meet the following criteria:

1. A “classical” syndrome and cancer that develops within 5 years of the diagnosis of the neurological disorder.
2. A “non-classical” PNS that accompanies a diagnosed neoplastic disease, which resolves or significantly improves after cancer treatment without concomitant immunotherapy.

3. A “non-classical” PNS with onconeural antibodies (well characterised or not) and cancer that develops within 5 years of the diagnosis of the neurological disorder.
4. A neurological syndrome (“classical” or “non-classical”) with well characterised onconeural antibodies (anti-HU, -Yo, -CV2, -Ri, -Ma2, anti-amphiphysin), and no cancer.

Possible PNS has to meet the following criteria:

1. A “classical” PNS, with no onconeural antibodies, and no cancer, but at high risk to have an underlying tumour.
2. A PNS (“classical” or not) with partially characterised onconeural antibodies, and no cancer.
3. A “non-classical” neurological syndrome, with no onconeural antibodies, and cancer present within two years of diagnosis.

Individual neurological syndromes differ in terms of their symptoms, course of the disease, and response to treatment, but there are some common denominators, including the rapid symptom progression (from several days to several months), and significant neurological deficit. The patient's clinical condition stabilizes with time, but the symptoms are multifocal, and there are some typical locations of the nervous system damage, including the limbic system, cerebellum, brain stem, and dorsal root ganglia [1].

PNS is a rare diagnosis (involving around 1% of neoplastic diseases), but in some cancers they are reported significantly more frequently. In the course of breast cancer, the literature has reported cases of subacute cerebellar degeneration, stiff person syndrome (SPS), opsoclonus-myoclonus syndrome, paraneoplastic retinopathy, and acute necrotizing myopathy [3, 9].

SPS is one of the non-classical paraneoplastic syndromes, and is also associated with conditions whose aetiology is other than neoplastic [1, 2, 10]. The primary symptoms of SPS include deep muscular rigidity in the region of the spine and extremities, and paroxysmal painful muscle spasms, triggered by sudden movement, noise, and emotional stress. In the majority of cases the pathogenic background is an autoimmune reactions involving the production of anti-glutamic acid decarboxylase antibodies (anti-GAD) [1, 2, 9, 10]. Anti-GAD antibodies are also observed in the course of metabolic diseases, and diabetes in particular.

SPS has also been reported as accompanying breast cancer and small-cell lung carcinoma. Apart from the anti-GAD antibodies, the syndrome also involves anti-amphiphysin antibodies, i.e. antibodies against the protein present in nerve endings, whose function is connected with the endocytosis process.

Slight differences are observed in the clinical picture of the syndrome, depending on the type of antibodies. In the case of anti-amphiphysin antibodies, the stiffness mainly involves the neck and shoulder girdle, while in the anti-GAD syndromes it is located within the thoracic muscles and lumbar spine. The stiffness is often extremely intense and painful. In paraneoplastic syndromes, stiffness is often the main symptom, but it is of varying intensity. Response to treatment is also different. In anti-amphiphysin syndromes, there is hardly any improvement, following the administration of high immunoglobulin doses (contrary to anti-GAD syndromes). Treatment involves glucocorticosteroids and plasmapheresis. In both syndrome types, though, improvement is observed after high doses of benzodiazepines (diazepam 50 mg/day) [2].

## CONCLUSION

In summary, one should emphasise that the stiff person syndrome is very rarely diagnosed as a non-classical paraneoplastic

syndrome, and if so the prognosis is poor. Diagnostics based on the analysis of clinical symptoms solely is difficult, and correct diagnosis requires numerous specialist examinations. Specific biological tests are needed in order to detect the antibodies involved. The ultimate diagnosis is often offered too late, when the neurological deficit is significant. Detection of paraneoplastic neurological syndromes may be conducive to an earlier diagnosis of cancer, but neurological improvement is rarely observed, regardless of the symptomatic treatment administered, including immunosuppression, glucocorticosteroids, plasmapheresis, and high doses of benzodiazepines. On the other hand, initiation of anti-cancer treatment may bring in neurological improvement, even though the neurological deficit is often irreversible.

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### Authors' contributions:

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Zofia Rusinowska: corrections  
Ewa Nowakowska-Zajdel: idea of the work, corrections