Otherwise, the most frequent cause of hemianopsia is vascular events, followed by trauma and brain tumor.[4] Consequently, a third hypothesis, the most accepted one, to explain macular sparing is a double vascularization of the posterior striate cortex. Posterior cerebral artery supplied occipital lobe by four branches (posterior temporal, anterior temporal, parieto-occipital and calcarine). Calcarine artery supplies the whole striate cortex in fifty percent of people.[2] The middle cerebral artery also supplies occipital lobe with the posterior temporal artery and the artery of the angular gyrus.[5] Another vascular explanation for macular sparing is bifurcation of posterior temporal artery before the calcarine artery. Occipital cortex could be supplied by the posterior temporal artery even if there is a thrombosis in calcarine artery. This explanation may be incomplete because posterior temporal artery supplies occipital cortex in only fifty percent of cases, but as we know, macular sparing is far of being a universal phenomenon in ischemic stroke.[2]

Many others hypotheses are written in literature, but to our opinion, the more relevant are listed above.

On the other hand, anticardiolipin antibodies are a cause of arterial and venous thrombosis. It is also known that anticardiolipin antibodies are frequently elevated in association with malignancy. In our case, we suppose that a hypercoagulable state is the cause of recurrent strokes in this patient.

In conclusion, we think this case illustrate one more proof that, at least in our case, macular sparing is more likely explained by a vasculature hypothesis or by a large representation of macular vision in striate cortex rather than by a bilateral occipital macular representation.

Anne-Marie Dufresne, Martin Savard
Quebec, QC, Canada

References

1. Steiner A. Homonymous hemianopia, bilateral with macular sparing, of vascular origin. Am J Ophtalmol. 1951;34(8):1170-3.
2. Leff A. A historical review of the representation of the visual field in primary visual cortex with special reference to the neural mechanisms underlying macular sparing. Brain Lang. 2004;88: 268-78.
3. McFadzean R, Brosnahan D, Hadley D, Mutlukan E. Representation of the visual field in the occipital striate cortex. Br J Ophthalmol. 1994;78:185-90.
4. Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. Homonymous hemianopias: Clinical–anatomic correlations in 904 cases. Neurology. 2006;66:906-10.
5. Tanaka R, Miyasaka Y, Yada K, Mukuno K. Bilateral homonymous hemianopsia due to temporal herniation, with sparing of central vision: Case report. Neurosurgery. 1992;31(4):787-91.

To the Editor

Paraneoplastic Encephalomyelitis, Stiff Person Syndrome and Breast Carcinoma

Paraneoplastic syndromes (PNS) are the rarest non-metastatic neurological complications of cancers in which no specific etiology can be identified. Among PNS, stiff person syndrome is characterized by "rock-hard" rigidity and painful spasms in distal limbs, most frequently legs, and abnormal foot and/or hand posture. General posture is rigid; ambulation is difficult and may result in falls. Paraneoplastic syndromes are postulated to be autoimmune diseases. Stiff person syndrome associated to cancer display high antibody titers directed against neuronal proteins[1,2].

We present the case of a woman first diagnosed with stiff person syndrome, which led to the diagnosis of an invasive ductal carcinoma of the breast. Paraneoplastic antibodies titers previously reported in literature were all negative.

Case Report

A 30-year-old woman presented to the hospital in October 2006 for involuntary muscle contractions of the legs, making walking difficult with occasional falls. Spasms were painful, waking her in the night, and it was possible to provoke them by applying pressure to the lumbar region. Legs and arms were stiff, legs being much worse. Spasms were treated with benzodiazepine with very minimal improvement.

The investigation included the following (in chronological order): cerebral magnetic resonance imaging (MRI), cervical/thoracic/dorsal MRI, electromyogram, electroencephalogram, lumbar/sacral MRI and mammography. Mammography revealed the presence of a mass and asymmetric density in her left breast. Percutaneous biopsy revealed an invasive ductal carcinoma, grade I/III, estrogen receptor-positive, progesterone receptor-positive and HER2-negative. Positron emission tomography revealed one metastasis in left internal mammary node chain and another one in left axillary region. There was no other metastasis.

Cerebral and spinal magnetic resonance imagery showed neither lesion nor metastasis. Lumbar puncture showed slightly elevated white cells count ($6x10^6$/L), but normal proteinorachia. The following anti-neuronal autoantibodies were performed and were all negative: anti-Hu, anti-Ri, anti-Yo (anti Purkinjee cells antibodies (ab)), anti-glutamic acid decarboxylase (GAD) ab, anti-amphiphysin ab, anti-CRMP-5 ab, anti-striated muscle ab, anti-P/Q-Type calcium channels ab, anti-N-Type calcium channels ab, acetylcholine receptor binding ab and anti-acetylcholine receptor ganglionic neuronal ab.

She received intravenous immunoglobulin (IVIG) treatment in November 2006 with no effect. Lumpectomy and axillary dissection were performed on December 11th, 2006. Pathology reports a T_2 $N_{1/18}$ M_0 invasive ductal carcinoma. Neurological symptoms were not improved following surgery. Gabapentin and clonazepam were added to treatment, improving spasms control

https://doi.org/10.1017/S0317167100018011 Published online by Cambridge University Press

but with little effect on limb stiffness. She received five plasmapheresis treatments with minimal improvement.

In December, after the surgery and despite plasmapheresis, new neurological symptoms developed rapidly in a few days, including spastic dysarthria, dysphagia, facial dystonia with a deformed smile, diplopia with bilateral horizontal gaze palsy and nystagmus. Pupils were normal. She never became confused or obtunded nor had seizure. There was diffuse spasticity with knee and ankle clonus and brisk jaw jerk. Sensory exam was normal. She could walk with aid but had stiff and painful legs, but no gait ataxia or incoordination on finger to nose testing.

Symptoms were relieved with the first FEC-100 (5-fluorouracil 500mg/m^2, epirubicin 100mg/m^2 and cyclophosphamide 500mg/m^2) chemotherapy cycle in January 2007. She then received two other FEC-100 cycles. Over the next few weeks, her stiffness gradually improved, the dysarthria disappeared and eye movement partially improved. She was discharged in early February 2007 with gabapentine 800mg q.i.d., citalopram 40mg q.d., clonazepam 0.5mg t.i.d. and baclofen 15mg q.i.d. treatments. On neurological examination in May 2007, speech was normal, there was no facial dystonia or dysarthria and eye movements were normal. Deep tendon reflexes were slightly brisk but plantars were normal. Strength was normal as well as sensory exam. Walking was minimally spastic but brisk.

Cancer treatment was completed using three docetaxel (100 mg/m^2) cycles and radiation therapy (46 Gy to left sus-clavicular area, 50 Gy to left breast and 46 Gy to left internal mammary node chain). Starting June 2007 and July 2007, she received tamoxifen and goserelin, respectively.

After three and-a-half years of follow-up, patient is now without cancer recurrence. Gabapentine, clonazepam and citalopram were progressively stopped. Baclofen treatment was continued. Legs are still slightly stiff, but she is able to walk rapidly without any help.

Discussion

Paraneoplastic syndromes are the rarest neurological complications of cancer and are defined as non-metastatic neurological complications in which no specific etiology could be identified, estimated to affect 0.01% of cancer patients[1,2]. Paraneoplastic syndromes include limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus-myoclonus syndrome, paraneoplastic retinopathy, stiff-person syndrome, motor neuron disease, peripheral neuropathy, neuromyotonia, Lambert-Eaton myasthenic syndrome, myasthenia gravis and inflammatory myopathies. Any portion of the central or peripheral nervous system can be affected. Though a very small percentage of cancer patients are affected, clinicians need to differentiate PNSs from the more common neurological disorders induced by metastases and cancer treatments. Paraneoplastic syndromes diagnosis depends mainly on clinicians' suspicion, which depends on their experience about neurological disorders in relation to types of cancer. Also, neurological symptoms may appear before any cancer symptoms or diagnosis[1,2], as in the present case.

Stiff person syndrome is characterized by the gradual onset of stiffness and rigidity, first in axial muscles and progressing to limb muscles. The legs are primarily involved. Antagonist muscles are continuously contracting and are described as rock-hard or board-hard at palpation. Electromyography shows continuous motor activity in affected muscles. Posture is rigid; ambulation is difficult and results in frequent falls. Patients also experience sudden and painful muscle spasms, often induced by touch, involuntary movement, sudden loud noise or stress[1]. Our patient not only had a paraneoplastic muscle stiffness and spacticity but also developed, despite plasmapheresis, signs and symptoms of brainstem dysfunction (paraneoplastic rhombencephalitis) with dysarthria and ophtalmoplegia.

Autoimmunity is postulated as being the cause for stiff person syndrome. Expression of some proteins normally restricted to neurons by cancer cells results in high titers of antibodies directed against these neuronal proteins. It was at first speculated that stiff person syndrome symptoms were induced by a failure of neuronal inhibitory functions[3]. This hypothesis was confirmed in stiff person syndrome patients by Solimena et al. with the observation of auto-antibodies against GAD, an enzyme essential to gamma-aminobutyric acid synthesis, an important inhibitory neurotransmitter[4]. A few years later, auto-antibodies against a protein later identified as amphiphysin were detected in stiff person syndrome with breast cancer[2]. Other auto-antibodies has been reported as associated to stiff man syndrome: anti-Ri in a patient with lung cancer and antigephyrin in a patient with mediastinal cancer. Most importantly, presence of paraneoplastic auto-antibodies is indicative of an underlying and maybe undiscovered cancer, not of a neurological syndrome[1].

Five percent of stiff person syndromes are associated to a cancer[5]. Non-paraneoplastic stiff person syndrome is associated in most cases to an auto-immune condition, such as primarily insulin-dependent diabetes mellitus, thyroiditis, vitiligo and pernicious anemia. Diabetes mellitus is present in most non-paraneoplastic anti-GAD-positive stiff person syndrome patients, but the reverse is not true, i.e. not all diabetic patients with GAD ab develop stiff person syndrome[1].

Discovery that antiamphiphysin ab transfer from stiff person syndrome patients to rats produced dose-dependent stiffness in the animals suggests direct ab pathogenesis[1]. Hence, IVIG were used and has been shown effective in two clinical trials on the non-paraneoplastic form of stiff person syndrome[1], while only a small number of case reports reported the use of IVIG in paraneoplastic stiff person syndrome[1,2]. Drugs that enhance GABA-ergic inhibition, such as benzodiazepines, reduce spasms without influencing the cause of the problem. Immunomodulation therapy is unlikely to replace the need for benzodiazepines in spasms control[1,2]. Clinical benefit has been reported following treatment for breast cancer. However, a series report neurological improvement in only 44% of patients following tumor treatment. Plasmapheresis has been reported as potentially helpful to treat the syndrome[1,2].

The case presented here was negative for a vast panel of antibodies known to be associated to paraneoplastic syndromes, including anti-GAD ab and anti-amphiphysin ab, which are associated to stiff-person syndrome. As outlined by Murinson[2], a number of patients present a clinical stiff-person syndrome without the known antibodies. It doesn't mean that autoimmunity is not involved, but rather that there is still unknown antibodies causing the syndrome. Treatment of the neurological symptoms was inefficient until the cancer, the cause

https://doi.org/10.1017/S0317167100018011 Published online by Cambridge University Press

of the symptoms, was treated. Since neurological presentation precedes cancer diagnosis in more than 70% of the cases[1,2], our case again illustrate the importance of considering the possibility of an occult malignancy in unexplained, atypical syndromes, even in younger patients.

Julie Lemieux, Louise Provencher,
Denis Brunet, Jean-Charles Hogue
Quebec City, QC, Canada

References

1. Toothaker TB, Rubin M. Paraneoplastic neurological syndromes: a review. Neurologist. 2009;15(1):21-33.
2. Murinson BB. Stiff-person syndrome. Neurologist. 2004;10(3): 131-7.
3. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. Am J Med. 1967;42(4):582-99.
4. Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med. 1988;318(16):1012-20.
5. Grant R, Graus F. Paraneoplastic movement disorders. Mov Disord. 2009;24(12):1715-24.

To the Editor

A Case of Phenytoin-Induced Encephalopathy in a Mathematician with Stage IV NSCLC

It is estimated that more than 1,000,000 prescriptions for phenytoin (dilantin sodium) are filled per year in Canada[1]. Phenytoin is a widely prescribed anti-epileptic agent and in the context of advanced cancer with brain metastasis, it is often used for seizure prophylaxis post-craniotomy and/or radiotherapy. However, toxicity due to phenytoin can be mistaken for signs of disease progression and can result in significant functional deterioration. We present the case of a 65-year-old mathematician with Stage IV NSCLC whose unidentified phenytoin-induced encephalopathy caused by an interaction with sulfamethoxazole and trimethoprim resulted in admission to palliative care. Withdrawl of phenytoin led to a remarkable return to functional baseline. This case serves as a cautionary tale for all clinicians whose patients are treated with this agent.

A 65-year-old mathematician with stage IV adenocarcinoma of the lung underwent successful surgical resections of two brain metastases in January 2009 after presenting with increasing confusion. The first 2.3 cm diameter lesion was located in the left occipital-parietal region at the cortico-subcortical junction and the second, 2.4 cm in diameter, was located in the right superior frontal gyrus. She was treated with dexamethasone and 300 mg phenytoin daily for seizure prophylaxis. In the immediate post-operative period, she experienced a single complex partial seizure involving her right arm, which resolved without intervention. It was then decided that she would remain on phenytoin prophylactically. She underwent a course of whole brain radiation (30 Gy in 10 fractions) and regained the ability to walk. Two months post-resection, the patient obtained a perfect score on the Mini-Mental Status Exam (MMSE). An magnetic resonance image (MRI) six months post-radiation revealed complete resolution of all brain disease.

In June 2009, the patient began treatment with gemcitabine for the primary lung tumour. At the time she was treated with 450 mg phenytoin daily and had a normal serum albumin. She remained seizure-free. However, after 11 courses of chemotherapy, the patient began to deteriorate neurologically. Chemotherapy was then terminated in November 2009.

Increasingly aphasic, the patient became incontinent and developed significant left-sided neglect with spasticity in her left foot that progressed proximally. An MRI brain and spine revealed no new metastasis. Electroencephalogram (EEG) revealed disturbance of cerebral background activity but no evidence of seizure activity. Other organic causes of the deterioration such as infectious or metastatic etiologies were ruled out. The patient then lost the ability to weight bear due to spasticity and significantly increased motor tone bilaterally with clonus in deep tendon reflexes. She exhibited delayed swallowing and was unable to follow commands. Disoriented and apraxic, she obtained 3/30 on the MMSE. Treatment at the time was supportive and an indwelling urinary catheter was installed to manage incontinence and recurrent UTI secondary to urinary retention. The installation of the catheter resulted in episodes of urinary infection with lethargy, nausea and vomiting. She responded well to repeated courses of Septra DS (180 mg trimethoprim and 800 mg sulfamethoxazole) and intravenous fluids. Her total phenytoin levels remained at the high end of normal (79-80 μmol/L) thoughout this period. Serum albumin was within normal range. In February 2010, the patient was admitted to palliative care for generalized deterioration thought to be due to urosepsis. In hospital, the delayed swallowing and lower limb spasticity resolved completely after a bolus of normal saline and the patient began conversing with hospital personnel. However, within one hour of the usual 200 mg phenytoin at bedtime, the patient was somnolent, with significantly increased spasticity. She was again unable to follow instructions. Given that the neurological deterioration appeared to be temporally related to the administration of phenytoin, a decision to stop the medication was made. The patient had been receiving phenytoin for one year at therapeutic levels.

Within two days of discontinuing phenytoin, the patient was again able to weight bear. She became increasingly conversant, identifying an obscure flower in a photograph. Spasticity in her lower limbs was resolved and swallowing function returned to normal. Within one week, the patient was able to walk 100 metres with a walker. She remained with a mild-moderate foot drop on the left with a positive Babinski reflex. The urinary catheter was discontinued and bladder retraining was begun. Within two weeks, her MMSE score was 27/30. The patient returned to previous activities including crosswords and Sudokus. With a proclivity for math, she began solving problems involving the binomial theorem and stated, when asked, the

https://doi.org/10.1017/S0317167100018011 Published online by Cambridge University Press