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CASE REPORT

PARANEOPLASTIC STIFF PERSON SYNDROME: INPATIENT REHABILITATION OUTCOMES OF A RARE DISEASE FROM TWO CANCER REHABILITATION PROGRAMMES

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Paraneoplastic stiff person syndrome is a rare, but debilitating, manifestation of cancer, characterized by painful extremities, truncal and facial spasms. The resultant functional impairment may necessitate comprehensive rehabilitation and symptom management. This case series describes the acute inpatient rehabilitation courses of 2 patients at different tertiary care referral cancer rehabilitation programmes, including work-up and diagnosis, medical management of symptoms, and functional outcomes. Both patients had a reduction in symptom burden and an improvement in motor function as a result of multidisciplinary acute inpatient rehabilitation.

Key words: stiff person syndrome; cancer rehabilitation; paraneoplastic stiff person syndrome; inpatient rehabilitation.

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INTRODUCTION

Stiff person syndrome (SPS) is a rare neurological disorder characterized by rigidity due to intermittent painful extremity, facial and truncal muscle spasms (1). SPS may be idiopathic or associated with other disease processes, including manifestation as a paraneoplastic phenomenon. The incidence of paraneoplastic SPS (PSPS) is unknown, but one study of 621 patients with SPS found that 10% were of the paraneoplastic variant; SPS has an approximate worldwide incidence of 1–2 cases per million (2). PSPS has been described as associated with multiple cancer diagnoses including breast, haematological, thymic, and lung (3). Due to the rarity of the disease, little is known about the rehabilitation process and outcomes of patients with PSPS. This case series provides a background on PSPS and describes the rehabilitation outcomes of 2 patients with PSPS at separate tertiary referral based cancer rehabilitation programmes. These represent the only cases of PSPS admitted to the acute inpatient rehabilitation unit at these institutions for the past 10 years.

SPS is thought to be related to an autoimmune process, as antibodies to glutamic acid decarboxylase (GAD), an enzyme that synthesizes gamma-aminobutyric acid (GABA), is found in up to 60% of people with SPS (4). Antibodies to amphiphysin, a synaptic vesicle protein, has also been described as an abundant autoantigen, sometimes associated with malignancy, suggesting that multiple pathways can be affected to produce the SPS phenotype (1, 5, 6). Imaging during work-up is often negative, and electromyography (EMG) may be normal or show continuous spontaneous discharges (7).

Patients with SPS are generally treated with some form of immunosuppression, including intravenous immunoglobulin (IVIg) (8), sometimes with favourable results, but often not with resolution of the disease. In PSPS, symptoms often improve and may resolve completely with treatment of the malignancy with which it is associated (1). The literature on symptom management is sparse, but diazepam is described as being effective for both SPS and PSPS, sometimes requiring doses of 40 mg/day (1). There are also reports of the benefits in using dantrolene (9), baclofen, and other medications that potentiate the effects of GABA. Botulinum toxin to truncal and facial muscles has been described as beneficial for focal muscle spasms refractory to oral and/or intrathecal medication (10, 11). No studies have evaluated the efficacy of pharmacological interventions for SPS/PSPS in a controlled manner, making it difficult for practitioners to know which medications and dosages to try (Table I).

Little is known about disability and the rehabilitation of this patient population, but 1 study that followed 35 SPS patients for 5 years found that most patients had at least mild disability (defined as a score of 2 or greater on the Rankin scale), and that 12 patients were permanently disabled due to SPS. Unfortunately, the interventions to improve mobility beyond pharmacological management were not described (1).

CASE REPORTS

Case 1

A 48-year-old woman presented with bilateral lower extremity aching pain that progressed rapidly to burning, numbness, and tingling over the course of one month. The work-up was broad, and included magnetic resonance imaging of her entire spine and brain, which were unremarkable. Electromyography revealed a non-length-dependent sensory neuropathy. Numerous serum and cerebral spinal fluid laboratory studies, including autoimmune antibodies and muscle enzymes, were negative,

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Table I. *Characteristics of stiff person syndrome*

Antibodies commonly found	Diagnostic tests	Physical findings	Disease treatment	Pain/spasm management (level of evidence)
GAD (SPS, less commonly PSPS) (1, 4) Amphiphysin (PSPS) (5, 6)	Imaging of brain and spinal cord normal EMG may show polyneuropathy and/or repetitive discharges (7)	Pain, stiffness, muscle cramps, weakness, gait difficulty. Lower extremities and trunk may be most affected	IVIg, or treatment of the underlying malignancy for PSPS (1, 8, 12) Complete resolution of SPS is uncommon, PSPS resolution may occur if malignancy is treated (1)	Benzodiazepines (numerous single cases) (1, 5, 7, 12) Baclofen (numerous single cases) (1, 10, 12) Dantrolene (case report) (9) Botulinum toxin (multiple case reports) (10, 11)

SPS: stiff person syndrome; PSPS: paraneoplastic SPS; GAD: glutamic acid decarboxylase; IVIg: intravenous immunoglobulin; EMG: electromyography.

except for positive cerebrospinal fluid (CSF) anti-amphiphysin antibodies, which supported the diagnosis of PSPS. Further work-up revealed a mass in her left breast and biopsy confirmed breast carcinoma. Intravenous immunoglobulin (IVIg) was administered for 3 days by the neurology service, with no relief of symptoms. Serum studies found to be negative/within normal limits were as follows: copper, B12, HIV antibodies, sedimentation rate, C-reactive protein (CRP), anti-neutrophil cytoplasmic antibodies (ANCA), anti-Gad65, Lyme disease antibodies, and ANCA. CSF studies negative/within normal limits included neutrophil count, lymphocytes, red blood cells, glucose, angiotensin converting enzyme (ACE), oligoclonal bands, venereal disease reference laboratory (VDRL), and anti-glutamic acid decarboxylase (GAD). Protein and albumin in the CSF were slightly elevated, at 85 mg/dl and 60.0 mg/dl, respectively.

The patient was given one dose each of doxorubicin and cyclophosphamide chemotherapy, and subsequently admitted to the acute inpatient unit due to profound disability and pain, requiring total assistance for lower extremity dressing, ambulation, wheelchair mobility, and all transfers, maximal assistance for bathing, moderate assistance for toileting, and supervision for grooming and bathing. Her pain, which made physical activity more difficult, worsened when she experienced frequent muscle spasms in her extremities. While on the acute inpatient rehabilitation unit, her pain and spasms were finally controlled with a combination of scheduled diazepam, 10 mg, and baclofen, 20 mg, both every 6 h, and gabapentin, 900 mg, 3 times a day. A second cycle of the same chemotherapy was initiated on day 12 of her stay on the acute inpatient rehabilitation unit, 14 days after the previous dose (Table II). She missed one morning of therapy due to fatigue after receiving the medication the previous night, but otherwise did not miss any therapy and tolerated chemotherapy well. Comprehensive rehabilitation consisted of a combination of stretching and strengthening with progressive resistance training, and an emphasis on transfers between a bed and a wheelchair and progressive work towards ambulation with assistive devices. Adaptive techniques with assistive reaching devices were initially employed to improve ADLs, particularly bathing and lower extremity dressing, and eventually she was able to perform these activities without assistive devices. Pressure-relieving ankle-foot orthotics were provided to prevent Achilles tendon contracture and decubitus ulceration over her calcanei.

During the patient's stay on the acute inpatient rehabilitation unit, her motor Functional Independence Measurement (FIM) scores improved (Table III) and she was able to discharge home at a modified independent level with a wheelchair and intermittent assistance from her parents. While she did improve in function and experienced reduction in pain in the days following the chemotherapy administered on the acute inpatient rehabilitation unit, it is unclear how much of her improvement can be attributed to chemotherapy and how much to the multidisciplinary rehabilitation programme and pharmacological management of her pain. Physical examination on the day of discharge demonstrated a significant increase in strength and reduction in tone; her upper extremity strength was 5/5 throughout, and lower extremity strength was essentially 5/5 except for right supine hip flexion (4/5) and left great toe extension (4/5). Her pain at discharge was controlled with 5 mg diazepam and 10 mg baclofen every 8 h. She continued outpatient physical and occupational therapy, and followed-up closely with her oncologist. Two months after discharge, she continues to use diazepam (5 mg as needed every 8 h), baclofen (10 mg every 8 h) and scheduled gabapentin (900 mg every 8 h) for spasm

Table II. *Background information on patients, diagnostic work-up, and treatment*

Case	Age, years	Cancer diagnosis	Antibodies associated	EMG findings	Anti-spasm/pain meds needed	Chemotherapy used during rehabilitation?
1	48	Breast	Amphiphysin	Sensory neuropathy	Diazepam 10 mg every 6 h Baclofen 20 mg every 6 h Gabapentin 900 mg every 8 h	Yes (doxorubicin, cyclophosphamide)
2	46	Breast	GAD65	Normal	Diazepam 10 mg every 12 h Baclofen 10 mg every 8 h fentanyl 25 μg/day Morphine 7.5 mg every 3 h	No

EMG: electromyography.

Table III. *Outcomes of acute inpatient rehabilitation*

Case	LOS	AdmitMotor	AdmitCog	DiscMotor	DiscCog	Change Mot	Change Cog	FIM efficiency
1	21	28	31	69	32	+41	+1	2.0
2	14	54	35	72	35	+18	0	1.3

FIM: Functional Independence Measure; LOS: length of stay; AdmitMotor: motor FIM scores on admission; AdmitCog: cognitive FIM scores on admission; DiscMotor: motor FIM scores at discharge; DiscCog: cognitive FIM scores at discharge. FIM efficiency is calculated as total (motor+cognitive) FIM gain divided by length of stay.

relief. Definitive treatment for her breast cancer, via mastectomy and possible adjuvant radiation therapy, is planned.

Case 2

A 46-year-old woman was diagnosed with left breast invasive ductal carcinoma that was initially treated at an outside facility with 6 cycles of neoadjuvant docetaxel, carboplatin and trastuzumab followed by maintenance trastuzumab every 3 weeks, for a total of 5 months of chemotherapy. She had a partial response, and approximately 7 months after initial diagnosis, she underwent a modified radical mastectomy and axillary lymph node dissection (4/15 lymph nodes were positive). At 10 months after initial diagnosis, she completed 5,040 centigray of radiation therapy in 28 fractions and was started on adjuvant tamoxifen. She subsequently moved to a new state and transferred her care to our institution (21 months after diagnosis).

Three months after moving locally, she presented to the orthopaedic surgery clinic with leg stiffness, and the clinicians thought the symptoms to be neurological in nature. Three months after that, in the neurology clinic, an initial autoimmune work-up was ordered, but she was lost to follow-up. At 28 months after initial diagnosis, she subsequently presented to the emergency department with worsening bilateral lower extremity stiffness, pain, and weakness without bowel or bladder dysfunction. She revealed that her father, who lives in a tropical country, had a similar lower extremity stiffness that was never diagnosed. She was subsequently worked up for the aetiology of her symptoms: tropical spastic paraparesis work-up was negative and antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) were negative. Muscles enzyme analysis was normal except for mildly elevated aldolase. Computerized tomography of the brain, thoracic, and lumbar spines were negative for metastasis, haemorrhage, or spinal canal stenosis. EMG was limited by pain tolerance, but was normal without evidence of hyperexcitability. A paraneoplastic antibody panel was sent, and serum anti-GAD65 was positive, yielding the diagnosis of PSPS in the setting of her history of breast cancer.

She was given 0.4 g/kg daily doses of IVIg for 8 days and diazepam starting at 10 mg orally daily and titrated up to 20 mg orally every 12 h. A repeat axillary lymph node biopsy was negative. She was also placed on long-acting oxycodone, 10 mg every 12 h, and short-acting PRN oxycodone, 5 mg every 3 h as needed. These treatments resulted in reduction of her muscle spasm-related pain from an 8/10 to 0/10. Her function also improved, from requiring total assistance for transfers upon admission to being able to ambulate modified-independently with a rolling walker for over 120 m at discharge. Given these improvements, she was discharged home with home physical and occupational therapy and a diazepam taper.

At approximately 30 months after initial diagnosis, a subsequent follow-up visit at the physical medicine and rehabilitation (PM&R) clinic 8 days post-discharge revealed worsening hypertonia after discontinuing diazepam as per the prescribed taper. She could no longer perform transfers or ambulate. Reinitiating the diazepam did not resolve her symptoms, and she was subsequently re-admitted to the hospital for worsening bilateral lower extremity stiffness 15 days later with 10/10 pain. IVIg at 0.4 g/kg daily for 8 days was again administered, diazepam increased to 10 mg twice daily, baclofen 10 mg thrice daily was started, and opiates changed to fentanyl transdermal patch, 25 mg every 72 h, with morphine immediate release, 7.5 mg every 3 h, as needed. Magnetic resonance imaging of the brain, cervical, thoracic, lumbar and sacral spine was negative for metastatic disease, spinal cord compression, or radiographic evidence of leptomeningeal disease. She again saw improvement in her pain to 0/10 and function to contact guard assist with transfers and ambulation walking 45 m with a rolling walker.

The patient was then transferred to the acute inpatient rehabilitation unit due to functional impairment without cognitive deficits. Ten days after transfer to the rehabilitation unit, she was given 70 units of onabotulinum toxin to her left quadriceps muscles using EMG guidance. With these interventions and interdisciplinary care, her symptoms and overall function improved (Table III), and she was discharged home on the above-described oral muscle relaxant and opiate regimen. She was discharged with a light wheelchair for long-distance mobility (she already had a rolling walker), a commode chair, and referrals for outpatient physical and occupational therapy.

DISCUSSION

Rehabilitation improved patient function in these 2 patients, and should be considered as part of the management of this rare disease process in the setting of physical impairment. This report is limited by the lack of statistical analysis, but the rarity of the disease made obtaining a larger sample size difficult. Given that there appears to be no other published data on rehabilitation of this disorder, these 2 cases may be helpful in guiding physiatrists who encounter this uncommon manifestation of cancer. This series is also limited by the fact that the 2 patients are similar in age and have the same cancer diagnosis; it is unclear if an older or younger population, or with a different associated cancer, would have similar outcomes.

Both patients in this report improved in overall function, as measured by Functional Independence Measure (FIM)

scores, with comprehensive interdisciplinary rehabilitation. Neither patient displayed significant cognitive impairment prior to arrival at their respective rehabilitation units. The first subject had lower motor function prior to admission, which may explain the larger gain and FIM efficiency compared with the second patient. Furthermore, the administration of chemotherapy during rehabilitation, which did not cause significant interruption to her therapy sessions, may have contributed to her overall improvement, given that the treatment of PSPS is treating the underlying malignancy. Management of spasms with GABA-modifying agents, such as diazepam and baclofen, appear to be effective, although complete resolution may not occur in the paraneoplastic variant of SPS unless the cancer is treated.

Finally, SPS should be considered in the differential diagnosis of patients with diffuse painful cramping when work-up for more common aetiologies is negative. When presenting in otherwise healthy adults, investigation for an underlying malignancy, or recurrence of a previously-treated malignancy, should be considered.

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