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CASE REPORT

Case Report: Breast cancer-associated paraneoplastic stiff person syndrome: anastrozole monotherapy insufficient for symptom improvement [version 1; peer review: 1 approved with reservations]

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Abstract

Stiff person syndrome (SPS) is a rare clinical disorder presenting with progressive muscle stiffness and painful spasms. Its ill-defined mechanism and variable presentation make diagnosis a challenge, though it is associated with a range of specific auto-antibodies. One particular antibody, anti-amphiphysin, is found in the presence of breast or lung malignancy and leads to a disorder termed paraneoplastic SPS (PSPS). Our patient, an 83-year-old woman, presented with bilateral leg weakness, spasms, and left clubfoot over a period of three months. She also reported a lump in her left breast for which she had not sought treatment over the past 10 years. Her ankle radiograph was negative for fractures and dislocations, while an MRI of the left leg was negative for plexopathies. Electromyography was suggestive of an SPS disorder and a positive anti-amphiphysin test indicated a diagnosis of PSPS. Her symptoms were managed with baclofen, diazepam, and five cycles of therapeutic plasma exchange (TPEX) over 10 days. Breast imaging revealed a 4.5-cm left breast lesion, later biopsy-confirmed as invasive ductal carcinoma (ER+, PR+, HER2-). The patient declined definitive surgical management, opting instead for once-daily anastrozole 1 mg as hormonal therapy. This regimen was not sufficient to lead to symptomatic improvement over a period of more than 30 days, and the patient expired less than 45 days after discharge. To our knowledge, this is the first case of PSPS to be treated in this manner. Our report illustrates that conservative management with anastrozole monotherapy was not sufficient to lead to symptomatic improvement in this form of paraneoplastic syndrome, suggesting the need for more aggressive pharmacological or definitive surgical intervention in order to produce symptom improvement

Open Peer Review

Approval Status ?

1

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 view

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 Health Science Center, Salt Lake City, USA

Any reports and responses or comments on the article can be found at the end of the article.

and/or resolution.

Keywords

Stiff person syndrome, Paraneoplastic, Invasive ductal carcinoma, Anastrozole

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Introduction

Stiff person syndrome (SPS) is part of an exceedingly rare spectrum of SPS disorders. Classic SPS presents with painful muscle spasms, increased sensitivity to stimuli, and gradual muscle stiffness, leading without intervention to spinal deformity and significant disability^{1,2}. Though the pathophysiology is poorly understood, it is often accompanied by the presence of anti-glutamic acid decarboxylase antibodies or anti-glycine receptor antibodies. In rare cases of breast and lung malignancy, it can present with anti-amphiphysin antibodies and is termed paraneoplastic SPS (PSPS)³. These antibodies have also been associated with paraneoplastic cerebellar degeneration⁴ and a rare presentation of SPS with transverse myelitis⁵, both of which are beyond the scope of this current discussion. We present a case of PSPS in the setting of occult breast malignancy. Current management typically involves a three-pronged approach consisting of immunotherapy, symptomatic control, and tumor eradication^{1,3}. Our case is unique in that our patient declined definitive surgical intervention and radiation, opting instead for conservative therapy with anastrozole. To our knowledge, this is the first such case to be treated in this manner. This article was previously presented as a virtual poster at the 2020 American College of Physicians Texas Chapter Meeting on November 7, 2020.

Case presentation

The patient was an 83-year-old Caucasian woman who presented with bilateral leg weakness, painful leg spasms, and left talipes equinovarus (Figure 1). Her symptoms started three months prior to presentation, but worsened rapidly and severely limited her ambulation. She was a retired postmistress and was most alarmed by her reduced mobility, as she transitioned from walking unassisted to using a cane and eventually to a wheelchair over a period of two weeks. Her past medical history included celiac disease and an unspecified thyroid disorder, while a review of her family history revealed two sisters with prior episodes of breast cancer. On physical examination, her cranial nerve exam was normal, as was her motor exam in the bilateral upper extremities. On examination of her lower extremities, however, 3/5 strength was noted in her proximal left lower extremity with 4+/5 on the right. She also showed 3/5 strength in ankle dorsal and plantar flexion on the left side, along with absent ankle reflex and extensor plantar response. She reported a lump in her left breast, present for the past 10 years. Further workup included a left ankle radiograph, which was negative for fractures or dislocations (Figure 2), a spinal MRI without evidence of plexopathy, a negative test for ganglioside antibodies, and a negative myositis panel. Electromyography showed spontaneous ongoing muscle activity at rest, and co-activation of agonist/antagonist muscle groups in the bilateral lower extremities, indicating a central process like SPS. She was given diazepam and baclofen for symptom relief and, after confirmation of positive neuronal anti-amphiphysin antibodies in the cerebrospinal fluid, the patient underwent five cycles of therapeutic plasma exchange (TPEX) over a period of 10 days. She did not report any functional lower leg improvement during this time. Breast imaging identified a 4.5-cm left breast mass (Figure 3), with regional spread to the left

Figure 1. Photograph of left lower extremity showing talipes equinovarus.

Figure 2. Left ankle radiograph showing no acute fractures or dislocations.

axillary lymph nodes but without distant metastasis. Pathology confirmed invasive ductal carcinoma (ER+, PR+, HER2-) with a Ki-67 index of 50%, grade T2cN3aM0, clinical prognostic stage IIIB. The patient declined chemotherapy and surgical resection, agreeing instead to hormonal therapy in the form of once-daily anastrozole 1 mg. She passed away less than 45 days after discharge without showing significant improvement in symptoms of PSPS.

Figure 3. Left breast mammography revealing a 4.5-cm lesion, later confirmed as invasive ductal carcinoma (ER+, PR+, HER2-).

Discussion

Despite the debilitating nature of PSPS, it is a clinically rare disorder without a clear delineation of optimal treatment practices. Disorders that fall upon the SPS spectrum have an estimated incidence of 1 case per million per year, but the paraneoplastic variant of the disease is particularly uncommon, comprising less than 10% of all SPS cases⁶. A review of current literature reveals a wide range of management options for PSPS, focusing primarily on treatment of the underlying malignancy and on symptomatic control. For muscle spasms and improvement in functional status, GABA agonists like diazepam or baclofen seem to be the preferred choice, though there is also a role for therapeutic plasma exchange and immunotherapy in refractory cases¹.

A myriad of approaches has been proposed for the treatment of underlying malignancy, based largely on the characteristics

of the cancer itself and on the condition of the patient. The management options range from surgical intervention alone, as one case report detailed drastic symptomatic improvement after tumor resection in a woman with PSPS⁷, while many others included an aggressive chemotherapy regimen with or without radiation therapy^{8,9}. One treatment plan coupled an intensive rehabilitation program with a regimen of chemotherapy, leading to significant symptomatic improvement in a matter of weeks¹⁰. The chemotherapeutic agents which appear to be favored are doxorubicin, docetaxel, and cyclophosphamide, though rituximab, carboplatin, and trastuzumab have also been reported^{8,10}. The major takeaway from the literature is that all reports of symptomatic improvement have included aggressive management of the underlying malignancy, whether through surgical resection, chemotherapy, radiation, or a combination of the three. No previous cases have reported on the use of anastrozole monotherapy in treating breast cancer-associated PSPS, which led us to report our results.

Conclusions

The case we present here is unique in that it developed from occult malignancy, present for as many as 10 years, and that the patient elected to pursue hormonal treatment of her breast cancer rather than definitive surgical or chemotherapeutic intervention. She unfortunately did not show any measurable symptomatic improvement on anastrozole, which we feel indicates a need for a more aggressive treatment regimen or a more prolonged course of hormonal therapy. In this particular case, anastrozole alone was not sufficient to produce clinical improvement or symptomatic resolution. To our knowledge, this is the first such report of breast-cancer associated PSPS to be treated with anastrozole and our hope is that it will be the grounds for further exploration of management options for this rare disease process.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

References

- Baizabal-Carvalho JF, Jankovic J: **Stiff-person syndrome: insights into a complex autoimmune disorder.** *J Neurol Neurosurg Psychiatry*. 2015; **86**(8): 840–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- McKeon A, Robinson MT, McEvoy KM, et al.: **Stiff-man syndrome and variants: clinical course, treatments, and outcomes.** *Arch Neurol*. 2012; **69**(2): 230–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Balint B, Meinck HM: **Pragmatic Treatment of Stiff Person Spectrum Disorders.** *Mov Disord Clin Pract*. 2018; **5**(4): 394–401. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Grativvol RS, Cavalcante WCP, Castro LHM, et al.: **Updates in the Diagnosis and Treatment of Paraneoplastic Neurologic Syndromes.** *Curr Oncol Rep*. 2018; **20**(11): 92. [PubMed Abstract](#) | [Publisher Full Text](#)
- Faissner S, Lukas C, Reinacher-Schick A, et al.: **Amphiphysin-positive paraneoplastic myelitis and stiff-person syndrome.** *Neurol Neuroimmunol Neuroinflamm*. 2016; **3**(6): e285. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Murinson BB, Guarnaccia JB: **Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease.** *Neurology*. 2008; **71**(24): 1955–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Manhalter N, Györfi O, Boros E, et al.: **Case report of a woman with anti**

amphiphysin positive stiff person syndrome. *Ideggyogy Sz.* 2017; **70**(5–6): 213–216.

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8. Kelly PA, Kuberski C: **Stiff person syndrome: a case report.** *Clin J Oncol Nurs.* 2014; **18**(4): 465–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Agarwal PA, Ichaporia NR: **Glutamic acid decarboxylase antibody-positive**

paraneoplastic stiff limb syndrome associated with carcinoma of the breast. *Neurol India.* 2010; **58**(3): 449–51.

[PubMed Abstract](#)

10. Smith SR, Fu JB: **Paraneoplastic stiff person syndrome: Inpatient rehabilitation outcomes of a rare disease from two cancer rehabilitation programmes.** *J Rehabil Med.* 2016; **48**(7): 639–42.
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This is a report of an 83 year old woman who presented with a longstanding breast mass, found to be an invasive ductal carcinoma, and with stiff person syndrome (SPS) associated with anti-amphiphysin antibodies detected in CSF. The major point of the manuscript (after the patient had failed plasma exchange) was that treatment of the tumor with anastrozole failed to produce improvement in the patient's SPS. The patient is an interesting one, and the manuscript is well-written and well-illustrated. One suspects that therapeutic options may have been limited by the patient's willingness to undergo treatment. However, there are several points where the manuscript would be improved.

1. The fact that the patient's SPS failed to improve on anastrozole is not surprising, and I am not sure that this point only – which is the main point of the manuscript – would be particularly helpful to the clinician treating such a patient.
2. It would be helpful to know why the patient died. Was it from her neoplasm, or from the SPS, or from some other cause?
3. The patient “declined chemotherapy”. Does this mean that the patient declined other antineoplastic chemotherapy, or immunotherapy, or both?
4. SPS, including paraneoplastic SPS, is an immune-mediated disease. I suspect that relatively few neurologists would limit therapy to antineoplastic therapy only. Again, it would be worth knowing if the treatment approach used was because the patient refused other modalities such as IVIG, corticosteroids, or rituximab. Ideally, how do the authors think this patient should have been treated?
5. The discussion covers tumor treatment fairly well. More detailed information should be given concerning the role of immunotherapy.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuroimmunology and remote effects of cancer on the nervous system

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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