Case Report

Delayed Neurological Paraneoplastic Syndrome from a Breast Carcinoma: A Case Report

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Abstract

Paraneoplastic neurological syndromes are a group of rare disorders triggered by an abnormal immune system response to a cancerous tumour. A woman with a breast carcinoma underwent neoadjuvant chemotherapy. This was followed by surgery, radiotherapy and endocrine therapy. Her co-morbidities were hypertension and diabetes mellitus. Eighteen months later, she presented with an acute onset of back pain with bilateral lower limb paraparesis. She had fever for 2 weeks prior to this. She was unable to walk and was confined to a wheelchair. She was anaemic with a haemoglobin of 7.3 g%. Spinal magnetic resonance imaging could not find any metastases. Cerebrospinal fluid analysis showed mild pleocytosis and absence of infection and malignancy. Whole body positron emission tomography computed tomography scan did not find any increased metabolic activity. Nerve conduction study showed electrophysiological evidence of generalised sensorimotor axonal polyneuropathy and bilateral subacute-chronic lumbosacral plexopathy. A paraneoplastic antigen autoimmune profile showed that the anti-amphiphysin was at borderline level. She was diagnosed to have neurological paraneoplastic syndrome and given intravenous methylprednisolone and immunoglobulin. Her lower limb weakness gradually improved. This case highlights the importance of recognising paraneoplastic markers like anti-amphiphysin in patients with breast cancer presenting with atypical, symmetric proximal weakness.

Keywords: Anti-amphiphysin; breast carcinoma; neurological paraneoplastic syndrome

Introduction

Historically, in the 19th century, it was observed that certain cancers caused various symptoms that were not due to direct tumour invasion or compression (1). These poorly understood conditions were called paraneoplastic syndromes (PNS) in the 1940s (2). It is estimated that PNS affect up to 8% of those with cancer (3). With a more recent understanding, PNS are attributed to tumour secretion of functional peptides and hormones (as in the case of endocrine PNS) or immune cross-reactivity between tumour and normal host tissues (as in the case of neurologic PNS) (4). Other systems that could be involved are haematology

and rheumatology. PNS have been commonly linked to non-small cell lung cancer, lymphoproliferative disorders, gynaecologic carcinoma and breast carcinoma. Excision of the underlying tumour often improves the condition (5).

Case report

A 44-year-old Para 1, presented with a right breast lump for the last 6 months. Examination revealed a 6 x 6 cm mass in the upper outer quadrant with an ipsilateral palpable axillary lymph node. She underwent a mammogram, breast ultrasound and a guided biopsy which confirmed the diagnosis of an invasive lobular carcinoma of the right breast, oestrogen receptor (ER) and progesterone receptor (PR) positive but Her2 negative. A breast magnetic resonance imaging (MRI) found the disease to be multifocal (m) with additional lesions at the retroareolar and upper pole (12 o'clock); but staging computed tomography (CT) thorax-abdomen and pelvis found no distant metastases; T3(m)N1M0. Her comorbidities were diabetes mellitus, hypertension and dyslipidaemia; which were diagnosed a few months later. Due to poor venous access, a chemoport was inserted and she underwent 6 cycles of chemotherapy (5-Fluorouracil, Epirubicin & Cyclosphosphamide followed by Docetaxel). A month later, she underwent surgery, a right breast wide local excision and axillary lymph node dissection. The histopathology report consisted of multifocal invasive lobular carcinoma; ypT3N1M0 ER+ PR+ Her2 negative. She underwent adjuvant radiotherapy to the right breast and supraclavicular fossa and was started on oral tamoxifen 20 mg daily.

Eighteen months later, she presented to the Emergency Department with an acute onset of back pain with bilateral lower limb paraparesis. The clinical onset was associated with significant proximal weakness, leading to difficulty rising from a seated position and frequent falls, accompanied by numbness in the feet. She was unable to walk and was confined to a wheelchair. She had loss of appetite and loss of weight amounting to 6 kg within 3 months. Neurological examination revealed sensorimotor deficit that primarily affected the proximal lower limbs with muscle power 3/5 over the hip flexion and normal over the distal muscles. There were absent deep tendon reflexes at the knees and ankles. While sensory symptoms showed some improvement with oral pregabalin (Lyrica), the proximal motor involvement persisted, with hip flexion power recorded between 3/5. She was anaemic with a haemoglobin of 7.3 g%. MRI of the spine revealed no evidence of metastatic disease. Furthermore, a whole-body 18F-FDG body positron emission tomography/computed tomography (PET/CT) scan demonstrated no focus of pathologically increased metabolic activity, effectively ruling out systemic malignancy or metabolically active recurrence (Fig. 1).

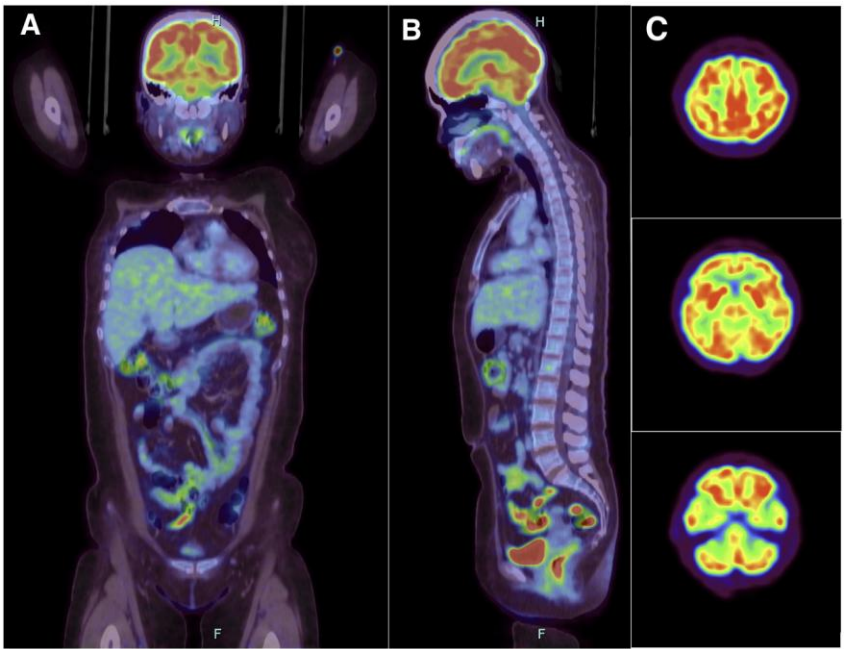


FIGURE 1: Whole body FDG positron emission tomography/computed tomography scan; A: Coronal, B: Sagittal, C: Axial (brain), showing normal distribution of FDG tracer

Cerebrospinal fluid (CSF) analysis demonstrated mild pleocytosis and an elevated protein level of 475 mg/L, in the absence of cytological malignancy or biochemical evidence of an infectious process. This finding, particularly the elevated protein without evidence of infection, supported an inflammatory or paraneoplastic aetiology. Nerve conduction studies (NCS) showed electrophysiological evidence of generalised sensorimotor axonal polyneuropathy and bilateral subacute-chronic lumbosacral plexopathy which confirmed an immune-mediated inflammatory attack and ruled out typical asymmetric diabetic damage (Table 1).

A paraneoplastic antigen autoimmune profile was done and the result obtained showed that the anti-amphiphysin (Amphi Ab) was at borderline level. This diagnosed her to have neurological paraneoplastic syndrome (NPNS). She was started on intravenous methylprednisolone 1 gram daily for 5 days followed by intravenous immunoglobulin therapy 0.4 g/kg daily for 5 days. Muscle power over the hip flexor improved to 4/5 and she was able to ambulate unaided after one month of treatment.

TABLE 1: Nerve Conduction Studies (NCS) and Electromyography

Sensory Nerve Conduction Studies				
Nerve / Sites	**Recording. Site**	**Latency (ms)**	**Amplitude (µV)**	**Velocity (m/s)**
R Median - Digit II (Antidromic)				
Wrist	Index	3.83	12.5	42
R Ulnar - Digit V (Antidromic)				
Wrist	Digit V	3.17	13.7	49
R Sural - (Antidromic)				
Calf	Ankle	3.90	3.6	38
L Sural - (Antidromic)				
Calf	Ankle	4.69	3.4	29
R Superficial peroneal - Ankle				
Lat leg	Ankle	NR	NR	NR
L Superficial peroneal - Ankle				
Lat leg	Ankle	NR	NR	NR
Motor NCS				
Nerve / Sites	**Muscle**	**Latency (ms)**	**Amplitude (µV)**	**Velocity (m/s)**
R Median - Abductor Policis Brevis (APB)				
Wrist	APB	3.75	12.2	
Elbow	APB	7.98	10.5	50
R Ulnar - Adductor Digiti Minimi(ADM)				
Wrist	ADM	2.54	10.0	
B.Elbow	ADM	6.48	9.3	46
A.Elbow	ADM	8.44	8.9	61
R Peroneal - Extensor Digitorum Brevis (EDB)				
Ankle	EDB	4.15	4.9	
B. Fib Head	EDB	13.88	3.7	34
A. Fib Head	EDB	15.77	3.4	32
L Peroneal - Extensor Digitorum Brevis (EDB)				
Ankle	EDB	4.58	2.8	
B. Fib Head	EDB	13.44	1.9	34
A. Fib Head	EDB	16.00	1.8	27
R Tibial - Adductor Hallucis (AH)				
Ankle	AH	5.17	12.8	
Knee	AH	16.35	9.4	33
L Tibial - Adductor Hallucis (AH)				
Ankle	AH	4.63	17.1	
Knee	AH	16.38	12.3	33
R Peroneal - Tibialis Anterior (TA)				
Fibular Head	Tib Ant	3.29	2.0	
Popliteal fossa	Tib Ant	4.75	2.1	41

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L Peroneal - Tibialis Anterior (Tib Ant)				
Fibular Head	Tib Ant	3.10	2.1	
Popliteal fossa	Tib Ant	5.23	2.0	42

Electromyography (EMG) study

Muscle	Nerve	Roots	Spontaneous			MUAP*		Recruitment	Interference
			IA	Fib	PSW	Amp	Dur.	PPP	Pattern
R. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	N	None	None	1+	1+	N	N
R. Gastrocnemius (Medial head)	Tibial	S1-S2	N	None	2+	1+	1+	N	Reduced
R. Vastus lateralis	Femoral	L2-L4	N	1+	2+	2+	2+	N	Reduced
R. Iliopsoas	Femoral	L2-L3	N	1+	2+	N	N	N	N
R. Lumbar paraspinals (low)		-	N	None	None	N	N	N	N
R. Lumbar paraspinals (up)		-	N	None	None	N	N	N	N
R. Gluteus medius	Superior gluteal	L4-S1	N	None	None	N	N	N	N

*Motor Unit Action Potentials are electrical signals recorded during EMG
N: Normal

Two months later she was diagnosed with septic shock secondary to a left emphysematous pyelonephritis with *E-coli* bacteraemia requiring an open left radical subcapsular nephrectomy. She recovered but developed renal failure requiring regular peritoneal dialysis. She has been planned to undergo an arteriovenous fistula surgery later to facilitate haemodialysis.

Discussion

With a history of breast carcinoma, sudden bilateral paraparesis should raise the suspicion of spinal metastasis causing cord compression. This is because bone is the most common organ to be affected by metastatic cancer (6). The highest prevalence of skeletal metastases has been documented to be in breast and prostate carcinoma (7). In this patient, the spinal MRI did not demonstrate any spinal metastases.

As she has diabetes mellitus, this should also be suspected as one of the possible causes of her paralysis. This may be a consequence of diabetic neuropathy, a form of nerve damage resulting from high blood sugar levels. Diabetic neuropathy affects various parts of the body and can lead to several types of paralysis; namely a severe form of peripheral neuropathy or proximal neuropathy also known as diabetic amyotrophy. However, presentation affecting bilateral paralysis in diabetics is not very common (8).

PNS involving the nervous system generally appear before the cancer has been identified (9). Contrary to the above information, in this patient, the PNS appeared 18 months after her breast cancer diagnosis and after she had undergone chemotherapy, surgery and radiotherapy. Neurologic PNS (NPNS) may affect any part of the nervous system. It may be divided based on the location of the syndrome: brain and cranial nerves, spinal cord, dorsal root ganglia, peripheral nerves, neuromuscular junction and muscle (9). NCS revealed generalised sensorimotor axonal polyneuropathy and bilateral lumbosacral plexopathy, indicating a widespread immune-mediated attack on the nerves. These findings strongly support a PNS aetiology over diabetic amyotrophy due to the symmetrical, bilateral involvement and the subacute, rapid progression of weakness. Furthermore, the presence of CSF pleocytosis confirms an active inflammatory process, which is characteristic of PNS but typically absent in diabetic nerve damage.

Anti-amphiphysin antibodies serve as highly specific biomarkers for underlying malignancies, most notably invasive carcinoma of the breast. Although traditionally linked to Stiff-Person Syndrome, these antibodies are also recognised markers for paraneoplastic encephalomyelitis and sensorimotor neuropathies.

Rojas-Marcos et al. (10) reported that in breast and gynaecological cancers, paraneoplastic cerebellar degeneration is the most frequent occurrence, followed by sensory-predominant neuropathy. For this second group, some had Anti-Hu antibody, and some had anti-amphiphysin antibody; as in this patient. However, the result of the anti-amphiphysin (Amphi Ab) although of borderline level, it was clinically appropriate with the diagnosis of neurologic PNS.

As PNS are immune mediated (4), the patient demonstrated clinical improvement in lower limb strength following treatment with intravenous methylprednisolone and intravenous immunoglobulin. However, these immunomodulatory therapies likely induced a state of secondary immunosuppression, predisposing her to the left pyelonephritis and subsequent bacteraemia. This infectious progression ultimately led to acute renal failure (11). This infective risk increased especially so as she is a diabetic (12).

Conclusion

PNS is an uncommon condition. The related malignancy is usually discovered during or after the PNS. However, in this case, the PNS was unusually diagnosed many months after excision of the malignancy and completing chemotherapy. Prompt diagnosis and treatment may improve clinical outcome and improve quality of life.

Conflict of interest: The authors declare no conflicts of interest.

Patient consent: The patient had consented to her case to be published.

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