Turkish Journal of Geriatrics
2016;19 (4):260-263

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Case Report

BREAST CANCER IN A WOMAN WITH GUILLAIN–BARRÉ SYNDROME: A REMINDER TO CONSIDER PARANEOPLASTIC NEUROLOGICAL SYNDROME

Abstract

A 72-year-old woman was referred to us for Guillain–Barré syndrome rehabilitation, during which her functional status improved (Hughes score 3–2, Functional Ambulation Classification Scale 2–4, Functional Independence Measure score 99–120). Despite her improvement, discharge was postponed because of a bloody discharge from her left nipple, which started 1 day before the last visit. The final diagnosis, after an excisional biopsy, was invasive ductal carcinoma with apocrine features. Guillain–Barré syndrome is an acute, rapidly progressing inflammatory polyneuropathy, with patients typically showing symmetrical, ascending weakness with a severe loss of reflexes. The current literature describes Guillain–Barré syndrome as a probable paraneoplastic neurological syndrome and cancer precursor. Guillain–Barré syndrome with this etiology, i.e., paraneoplastic neurological syndrome, may result from remote effects with immunological mechanisms that are not directly caused by the tumor or metastases infiltration. Guillain–Barré syndrome may develop as a paraneoplastic neurological syndrome, may be secondary to treatment, or may occur coincidentally with cancer. Because paraneoplastic neurological syndrome occurs at an early stage of cancer before metastasis, it is important to consider paraneoplastic neurological syndrome when evaluating Guillain–Barré syndrome patients.

Key Words: Breast Neoplasms; Guillain-Barré Syndrome; Paraneoplastic Syndromes

Olgu Sunumu

GUİLLAİN-BARRÉ SENDROMLU BİR KADINDA MEME KANSERİ-PARANEOPLASTİK NÖROLOJİK SENDROMLAR İÇİN BİR HATIRLATMA

Öz

Guillain-Barré sendromu saptanan 72 yaşındaki kadın hasta, rehabilitasyon amacıyla tarafımıza yönlendirildi. Rehabilitasyon sürecinde, fonksiyonel düzeyinde bir kazanım elde edildi (Hughes skoru 3'ten 2'ye, Functional Ambulation Classification düzeyi 2'den 4'de, Functional Independence Measure skoru 99'dan 120'ye değişim gösterdi). Bu gelişmeye rağmen, son vizitten bir gün önce sol meme ucundan gelen kanlı akıntı şikayeti nedeniyle taburcu işlemi ertelendi. Eksizyonel biyopsi sonucu nihai tanı apokrin özellik taşıyan invasiv ductal carcinoma olarak tanımlandı. Guillain-Barré sendromu akut, hızlı progresyon gösteren bir inflamatuar polinöropati dir. Bu hastalarda çoğunlukla reflex kaybının eşlik ettiği, simetrik, asendan güçsüzlük saptanır. Güncel literatürde, Guillain-Barré sendromu muhtemel paraneoplastik sendrom ve kanser öncüsü olarak tanımlanır. Bu tür bir Guillain-Barré sendromu, yani paraneoplastik sendrom; tümör veya metastaz infiltrasonunun doğrudan etkisi dışında, immünolojik mekanizmalara bağlı oluşan uzak bir etkiden kaynaklanabilir. Guillain-Barré sendromu; bir paraneoplastik sendrom olabilir, kanserle birlikte tesadüfi olarak veya tedaviye ikincil olarak gelişebilir. Bununla birlikte, paraneoplastik sendromun metastazlar oluşmadan önce, kanserin erken evresinde ortaya çıkması, Guillain-Barré sendromu olarak değerlendirilen tüm hastalarda paraneoplastik sendromu düşünmeyi elzem kılar.

Anahtar Sözcükler: Guillain–Barré Sendromu; Meme Kanseri; Paraneoplastik Sendrom.

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Received: 25/08/2016

Accepted: 17/10/2016

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Introduction

Guillain–Barré syndrome (GBS) is an acute inflammatory polyneuropathy that leads to numbness in the extremities, paresthesia, muscle weakness, and pain. It is characterized by progressive, symmetrical ascending weakness and loss of reflexes. Even when treated, GBS has a mortality of about 5%. The pathophysiology of this idiopathic peripheral nervous system disease is not well understood. It occurs rarely after administration of medication or vaccines or after surgery. The majority of GBS cases occur after respiratory or gastrointestinal infections (1).

Paraneoplastic neurological syndrome (PNS) occurs in malignancies and can present as peripheral neuropathy (2). GBS has been reported in patients with various malignancies, including leukemia, lymphoma, and colorectal, esophageal, breast, and small-cell lung cancer. It is not clear whether such cases of GBS are coincidental or are reflective of PNS (3-6). However, the current literature suggests that a case of GBS may be seen as a "probable" PNS and thus a precursor of cancer (7). We present a case in which breast cancer was detected in a patient undergoing rehabilitation for GBS. Our aim is to raise the level of sensitivity to PNS because clinicians tend to overlook this possibility.

Case Report

A 72-year-old woman with a history of upper respiratory tract infections was referred for GBS rehabilitation. She presented initially with an extensor weakness of the third phalange of the right hand, followed by weakness of the feet and hands manifesting on the same day, and was admitted to our neurology department. There was no evidence of any pathology on cervical magnetic resonance (MR) and diffusion-weighted MR imaging. Electromyography (EMG) revealed sensorimotor polyneuropathy characterized by axonal degeneration in the lower extremities. Following treatment with immunoglobulin for GBS, her clinical status stabilized and she was transferred to our clinic for rehabilitation. Initial physical examination revealed areflexia and symmetrical bilateral weakness in both upper (elbow flexion and extension 4/5, wrist extension and finger flexion 3/5) and lower (hip, knee, and ankle flexion and extension, 3/5, 4/5, and 4/5, respectively) extremities. No sensory impairments were noted. Laboratory findings were normal except for anemia (Hb = 9.4 g/dL). The patient did not consent to endoscopy and colonoscopy to investigate the cause of anemia. The patient's functional status improved during rehabilitation (Hughes score 3–2, Functional Ambulation Classification Scale 2–4, Functional Independence Measure score 99–120). Despite her improvement, discharge was postponed because of a bloody discharge from her left nipple that began 1 day before the last rehabilitation visit. Bilateral breast ultrasound revealed irregular contours of the left breast ducts and an intense, heterogeneous appearance of the entire outer quadrant of glandular tissue. Mammography detected a suspicious lobular pathology in the left breast, but could not exclude mastitis. A smear preparation of the nipple secretion was diagnosed with malignant cytology. Dynamic contrast-enhanced MR mammography detected a mass with asymmetric opacity in the left breast (ACR-BI RADS 4c). A Tru-Cut® biopsy of this area was diagnosed as atypical apocrine hyperplasia suspicious for *in situ*/invasive carcinoma. The final diagnosis on excisional biopsy was invasive ductal carcinoma with apocrine features.

Discussion

Despite appropriate treatment, disability or even death occur in approximately 20% GBS cases. Accurate diagnosis of GBS in the acute period is vital. The Brighton Collaboration GBS case definitions and guidelines include recommendations for the collection of patient data related to diagnostic certainty. Clinical case definitions are graded in four levels with level 1 as the most certain diagnosis (Table 1) (8, 9).

Because our patient was on anticoagulant therapy, we did not perform a lumbar puncture for evaluation of cerebrospinal fluid (CSF). However, electrophysiological findings of sensorimotor polyneuropathy characterized by axonal degeneration in the lower extremities were consistent with GBS. The EMG findings satisfied neurophysiological criteria that supported acute motor and sensory axonal neuropathy, in which the neurological deficits are both sensory and motor (10). At the same time, alternative diagnoses of weakness, diseases affecting the brain, spinal cord, and peripheral nerves or neuromuscular junctions and muscles were excluded. For our patient, the diagnostic certainty was determined to be Level 2 (Table 1). She had bilateral, flaccid weakness of the limbs, areflexia, a monophasic illness pattern, i.e., weakness that did not continue to worsen after the first 9 weeks of disease, electrophysiological studies consistent with GBS, and absence of an alternative diagnosis of weakness.

Cancer can lead to dysfunction of the peripheral nervous system, with peripheral neuropathy related to adverse effects of treatment (chemotherapy or radiotherapy) or to local inva-

Table 1— Brighton Collaboration Diagnostic Criteria and GBS Case Definitions (8,9).

Diagnostic Features	Diagnostic Certainty			
	Level 1	Level 2	Level 3	Level 4
1. Bilateral and flaccid weakness of the limbs	+	+	+	+/-
2. Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
3. Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days, subsequent clinical plateau	+	+	+	+/-
4. Electrophysiological findings consistent with GBS	+	+		+/-
5 and 6-CSF albuminocytological dissociation	+			+/-
5. Elevation of CSF protein level above laboratory normal value	+	+/-		+/-
6. CSF total white cell count <50 cells/ìl	+	+		+/-
7. Absence of an identified alternative diagnosis for weakness	+	+	+	+
	1+2+3+4+5+6+7	1+2+3+4+6 or 4+7	1+2+3+7	7

CSF: cerebrospinal fluid.

sion by malignant cells (11). Cancer may also cause PNS, which consists of remote effects with immunological mechanisms that are not directly caused by the tumor or metastases. PNS is rare, detected in fewer than 1/10,000 patients (12, 13), and the presence of a cancer etiology varies with neuropathy type. The involvement of cancer was observed in 47% sensory neuropathies, but in only 1.7% GBS cases. PNS may involve the central and peripheral nervous systems, and its severity has been attributed to inflammatory processes that can cause irreversible destruction of neural structures (14).

The definitions and diagnostic criteria of PNS include a group of "classical" syndromes that are often associated with cancer (e.g., subacute sensory neuronopathy and chronic intestinal pseudo-obstruction). The finding of a classical syndrome requires a search for a hidden malignancy even if onconeural antibodies not detected. GBS is seen as a "non-classical" PNS, and is a member of a subgroup of acute sensory–motor neuronopathies. It is not affiliated with well-known onconeural antibodies such as anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin (2). PNS is determined to be either definite or possible, classical or non-classical, by specific diagnostic criteria (Table 2). These are the time between cancer diagnosis and neurological disease diagnosis, improvement of neurological disease after treatment of cancer, and the presence or absence of onconeural antibodies. A non-classical PNS with absence of onconeural antibodies, and a cancer diagnosis within 2 years can be considered to be a "possible" PNS, i.e., possibly related to cancer (2).

Because of the diagnosis of GBS, our case was a non-classical PNS. We were not able to determine whether onconeural antibodies were present, but Graus et al. (2), propose testing for onconeural antibodies only if cancer has not yet been detected. Furthermore, absence of these antibodies cannot rule out a diagnosis of PNS. We diagnosed breast cancer in our patient within 2 months of diagnosing GBS. Given the nature of this case, we accept it as a possible PNS.

In a prospective multicenter study that included 979 patients with PNS, the most common neoplasias were small-cell lung cancer, ovarian cancer, breast cancer, and non-small-cell lung cancer. When PNS was diagnosed; 262 patients had local cancer, 360 had regional cancer, and 150 had metastatic cancer. These results indicate that PNS developed in the early stages of cancer or in cancers with limited spread (4). In fact, PNS can occur months or years before the cancer is diagnosed (13). However, another study interpreted 16 PNS cases as acute inflammatory polyradiculoneuropathy and coincidentally associated with cancer (7). Cancer and GBS were diagnosed simultaneously in seven of 435 GBS patients. The group was followed up for 9 years, and nine additional patients were diagnosed with cancer within 6 months. In that group of GBS patients, the incidence of cancer was found to be higher than that expected in the normal population (6). A study of PNS in gynecological cancer patients revealed four of the 45 breast cancer cases with possible PNS and two with GBS. One case of GBS appeared simultaneously with, and the other appeared 4 months after, the breast cancer diagnosis (15).

Table 2— Diagnostic Criteria for Paraneoplastic Neurological Syndromes (PNS) (2).

	Diagnostic Criteria			
	Type of Neurological Syndome	**Cancer Development Time**	**Improvement After Cancer Treatment**	**Onconeural Antibodies**
Definite PNS	Classical*	Within 5 years	-	-
	Non-classical**	-	+	-
	Non-classical	Within 5 years	-	+ (well characterised *** or not)
	Classical or Non-classical	-	-	+ (well characterised)
Possible PNS	Classical	-****	-	-
	Classical or Non-classical	-		+ (partially characterise)
	Non-classical	Within 2 years		-

*: Encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsodomus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstuction, Lambert-Eaton myasthenic syndome, Dermatomyositis
**: Acute sensorimotor neuropathy (GBS, brachial neuritis), subacute or chronic sensorimotor neuropathies...
*** anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin
****: no cancer, but at high risk to have an underlying tumor

In conclusion, GBS may develop as a PNS, may develop secondary to treatment, or may be coincidental with a cancer diagnosis. This is open to debate. However, as PNS occurs in early stage cancers and before metastasis, it is important to consider GBS as a possible PNS.

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