Guillain–Barré syndrome in a cancer patient treated with bevacizumab

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Abstract

We describe a case of Guillain–Barré syndrome (GBS) in a patient treated with bevacizumab. Our case is a 60-year-old woman with Stewart–Treves syndrome (STS), and angiosarcoma of her left forearm, with onset 12 years after diagnosis with stage IIIA left breast cancer. She suffered from repeated distal metastases including skin, bone, and liver metastases. She underwent numerous treatments including left arm amputation, radiation, and chemotherapy, but her disease was resistant. Thereafter, she received bevacizumab. Two weeks following the first administration, she presented in poor physical condition. Although the cause was not specified at that time, bevacizumab was discontinued. At 1 month following first bevacizumab administration, she gradually developed dyspnea, and numbness in her tongue and hands. Soon after, she was emergently admitted to the hospital due to hyperventilation syndrome. On hospital day 4, she developed quadriparesis, and on hospital day 8, she was diagnosed with GBS following neurological testing. Treatment with intravenous immunoglobulins was started immediately upon diagnosis, and her neurological symptoms eventually resolved. A repeat challenge course of bevacizumab was avoided. Five months later, the patient perished from STS progression. GBS associated with malignancies and/or chemotherapies has been rarely described in patients with malignant lymphomas. Of note, there is only one reported case of GBS with bevacizumab. Furthermore, in some cases, GBS is lethal, and it should be considered in the differential diagnosis of patients treated with bevacizumab.

Keywords Guillain–Barré syndrome · Bevacizumab · Breast cancer · Stewart–Treves syndrome

Introduction

Neurological disorders, including brain metastases and peripheral neuronal damage induced by chemotherapeutic agents, are often observed in patients with advanced cancers. Neurological manifestations of paraneoplastic syndromes (PNS), such as cerebellar degeneration triggered by immune response to a neoplasm, are occasionally reported. Guillain–Barré syndrome (GBS) was first described in 1916 [1]. GBS is a rare, severe, and acute paralytic neuropathy, occurring a rate of 1.11 cases per 100,000 person-years [2]. Elevated protein in the cerebrospinal fluid is essential for diagnosing GBS, whereas the cells are absent [3].

A relatively symmetrical flaccid motor neuropathy is characteristic of GBS, and patients frequently exhibit damaged deep tendon reflexes and facial nerve paralysis [4, 5]. Sensory deficits are not among the condition's marked features. Almost 30% of GBS cases are preceded by infection with *Campylobacter jejuni* [5]. *Cytomegalovirus* has been identified as a causative agent in up to 10% of cases [6].

The prognosis of GBS is relatively good, with 80% of patients with GBS recovering completely, and a mortality rate of only 5% [2]. Intravenous immunoglobulins and plasma exchange can further improve the prognosis. In addition, the early diagnosis is associated with better disease outcomes. GBS is reported as a concurrent condition in some patients with lymphoma [7], leukemia [7], small cell lung cancer [7], bladder cancer [8], breast cancer [9], and colon cancer [10]. Some of these develop as a PNS. GBS is not considered a classical PNS as no definite onconeural antibodies have been identified [11]. The association of GBS with malignancies remains controversial. In this report, we

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describe a case of GBS in a patient with Stewart–Treves syndrome (STS), treated with bevacizumab.

Patients and methods

The patient with advanced scirrhous breast cancer [invasive ductal carcinoma, estrogen receptor (–), progesterone receptor (–)] with STS visited to our department in December, 2015. A nerve conduction study was carried out by Neuropack S1 (NIHON KOHDEN CORPORATION, Tokyo, Japan). Twelve onconeural antibodies including Tr, GADD65, Zic4, Titin, SOX1, recoverin, Hu, Yo, Ri, Ma2/Ta, CV2, and amphiphysin were examined by EUROLINE® (Cosmic Corporation Co., Ltd. Tokyo, Japan). Examination of anti-gangliosides antibodies was conducted according to methods developed by Kindai University, which are described elsewhere [12].

Case report

A 60 year-old female presented for treatment of residual skin metastases of angiosarcoma on her left shoulder in December 2015 (Fig. 1). Her present illness began as a left breast cancer in 2000. She underwent a left mastectomy and axilla lymph node dissection with perioperative chemotherapy including cyclophosphamide, vinorelbine, and 5-fluorouracil, but detailed data pertaining to her clinical course were not available. She reported feeling persistent edema of the left upper limb following surgery, for which she visited her family doctor.

In February 2012, she noted swelling of the left aspect of the back of her hand and presented to an oncology specialist in May who subsequently diagnosed her with STS. The upper limb skin tumor was an angiosarcoma, and she opted to undergo amputation of her left upper limb, after which she received adjuvant taxane based chemotherapy.

Fig. 1 Histopathological features of the STS angiosarcoma in this case; **a** hematoxylin and eosin staining. **b** Immunohistochemistry of CD31. **c** CD34, **d** D2-40. CD31, CD34, and D2-40 are markers of angiosarcoma [13, 14]

She experienced recurrence within a single abdominal lymph node in December 2013, but the node was successfully resected. She started chemotherapy with paclitaxel, but unfortunately presented with a local recurrence on her left shoulder on June 2014, which was subsequently resected. Her chemotherapy was changed to eribulin, but the local recurrence appeared yet again, and was resected once more. Residual tumor cells were apparent in the border of the resected specimen, and the patient opted for additional chemotherapy in December 2015. By this time, metastases were apparent on her left shoulder and lateral thoracic region, and she was treated with extra-beam radiation [60 Gy/30 Fraction (Fr)]. She was subsequently treated with pazopanib, but this failed by April 2016 with the progression of skin lesions that were treated with additional extra-beam radiation (6 Gy/3 Fr, 54 Gy/27 Fr). She started chemotherapy with gemcitabine, but failed by October. Her uncontrolled skin lesions were then treated using an electron beam (40 Gy/20 Fr). The lesions spread to other skin, the liver, and bone (Fig. 2). To control these metastases, she began treatment with bevacizumab in November 2015, but was soon stopped secondary to the patient's poor physical condition. No apparent symptoms were observed and the cause of this situation was not specified at that time.

In mid-December, just 1 month after administration of bevacizumab, she began to experience dyspnea, and developed numbness of her tongue and hands. Soon after, she was emergently admitted to the hospital due to hyperventilation syndrome. She was not hypoxic, and blood gas analysis revealed the following: P_aO_2 126.5 mmHg, P_aCO_2 19.6 mmHg, pH 7.593, HCO_3^- 18.5 mmol/L, and base excess 0.4 mmol/L. The laboratory data are presented in Table 1. By hospital day 4, she was unable to walk unaided. The day after, she fell down while walking, and by hospital day 6, she could not lower her underwear and her right arm appeared paralyzed. She was unable to get up by herself, developed quadriparesis, and could not swallow. Her deep tendon reflexes were decreased to absent. By hospital day 8, GBS was suspected.

Nerve conduction testing, cerebrospinal fluid examination, and symptom observation confirmed the diagnosis of GBS (Tables 2, 3). Nerve conduction studies revealed prolonged distal latencies and decreased motor conduction velocities. This case was judged to be a demyelinating subtype and no onconeural antibodies were detected (Table 4). Concurrent brain computed tomography and magnetic resonance imaging revealed no new-onset vascular lesions without stable bone metastases in the left temporal bone, and no brain metastases.

She was immediately treated with intravenous immunoglobulins (IVIg, dosage; 20 g/body/day) and heparin (2000 U/body/day), continuing for 5 days. Her neurological symptoms gradually improved; by the sixth day following

onset, she was able to swallow again, and by 3 weeks, she could walk. Two months post-onset, testing was negative for GBS. She avoided a re-challenge of bevacizumab, but was treated with albumin-conjugated paclitaxel for 1 month, and then treated with doxorubicin twice. Unfortunately, these treatments were not effective. Five months following her GBS episode, she perished secondary to STS progression.

Discussion

GBS can be diagnosed clinically and this case was matched to Brighton criteria [4]. Nerve conduction studies are helpful for diagnosis, and can discriminate between axonal and demyelinating GBS subtypes [15]. In this case, we also observed a cytoalbuminological dissociation between the normal cell count and increased protein levels in the cerebrospinal fluid. The results of examination of anti-gangliosides antibodies are presented in Table 5. Among the antibodies, only galactocerebroside immunoglobulin G (Gal-C IgG) was positive. This supports our determination of this case demonstrating a demyelinating GBS subtype [16]. GBS solely positive for Gal-C IgG is rarely reported, and the relationship to the preceding mycoplasma infection is discussed [12]. However, in this case, we did not observe signs of infection or bone marrow dysfunction in the 3 months prior to symptom onset. The demyelinating subtype of GBS usually is associated with a good prognosis [15], and the patient's symptoms improved following standard treatment.

There are a few publications that discuss the link between advanced cancers and GBS. Vigliani pointed out a possible relationship between GBS and some cancers [7]. In cancer patients, GBS differs from the typical presentation in terms of mortality rate and severity. Among patients with cancer, the mortality rate associated with GBS is 22%, whereas that of typical GBS is 5.6% [7]. The median severity of GBS in patients with cancer is Grade 4, whereas that of the usual GBS is Grade 3, as judged by Hughes' scale [7]. Aside from these discrepancies, cancer-associated GBS and typical GBS are very similar. The therapeutic sensitivity for GBS in cancer patients is better, while the cancerous lesions still exist. On the other hand, PNS is often difficult to treat. In this case, GBS improved, while her cancer gradually progressed. This observation leads us to speculate as to the fundamental nature of GBS in patients with cancer. Although GBS has been described in patients with breast cancer [9], there are no reports concerning comorbid GBS and STS, or GBS and angiosarcoma.

In this case, we treated the patient with bevacizumab alone, as this agent is effective on both breast cancer and angiosarcoma [17, 18]. Bevacizumab was used just once, but it might have caused GBS, judging from the duration of treatment and the onset. There is only one report

Fig. 2 Cancer progression imaging of this case; **a** Skin metastasis in the left chest wall. **b** Skin metastasis in the back. **c** Liver metastasis; **d** bone metastasis in the left temporal bone (December, 2016)

describing GBS following bevacizumab administration in a patient with gliosarcoma. However, in that case, *Campylobacter jejuni* infection due to slight leucocytopenia

caused GBS [19]. In our case, there were no signs of infection. This report may suggest a direct link between bevacizumab and GBS, although further investigations are necessary to conclude definitely.

Table 1 Laboratory data during hospitalization

WBC (/μl)	7700	PT (s)	10.6	T.Bil (mg/dl)	0.6
neut (/μl)	5.650	PT INR	0.96	D.Bil (mg/dl)	0.1
eosi (/μl)	190	APTT (s)	27.9	BUN (mg/dl)	13.7
baso (/μl)	20	FDP (μg/ml)	8.3	Cre (mg/dl)	0.47
mono (/μl)	610	Fibrinogen (mg/dl)	468	UA (mg/dl)	3.9
lympho (/μl)	1240	D dimer (μg/ml)	3.29	CK (U/l)	70
RBC (/μl)	4.49×10^6	AST (U/l)	31	Na (mEq/l)	138
HGB (g/dl)	13.3	ALT (U/l)	26	K (mEq/l)	4.1
Hct (%)	38.3	ALP (U/l)	231	Cl (mEq/l)	104
MCV (fl)	85.3	LDH (U/l)	352	Ca (mg/dl)	9.1
MCH (pg)	29.6	GGTP (U/l)	32	iP (mg/dl)	3.0
MCHC (%)	34.7	TP (g/dl)	7.4	Glucose (mg/dl)	114
Plt (/μl)	1.57×10^5	Alb (g/dl)	4.0	CRP (mg/dl)	0.71

Table 2 Nerve conduction testing results

Nerve	Distal latency (m/s)	CAMP (distal/proximal, mV)	MNCV (m/s)
rt median	10.7	0.43/0.35	32.9
rt ulner	5.06	1.7/1.3	55.9
rt peroneal	16.8	0.26/0.15	31.1
rt tibial	6.95	1.61/0.72	35.5
Measured at 28.12.2016			
rt median	10.1	1.20/0.53	17.4
rt ulner	5.98	1.8/1.8	48.7
rt peroneal	22.5	0.71/0.23	26.6
rt tibial	10.1	1.53/1.50	43.1
Measured at 18.01.2016			

rt right, CAMP compound muscle action potential, MNCV motor nerve conduction velocity

Table 3 Cerebrospinal fluid examination results

Color	Colorless, clear
Pressure (mmH ₂ O)	120
Number (/mm ³)	2/3
Protein (mg/dl)	84
Glucose (mg/dl)	64

Table 4 Onconeural antibody expression

La	Tr	GAD65	Zic4	Titin	SOX1	Rec	Hu	Yo	Ri	Ma2/Ta	CV2	Amp
–	–	–	–	–	–	–	–	–	–	–	–	–

Rec recoverin, Amp amphiphysin

Table 5 Anti-gangliosides' antibody results

	IgM	IgG	IgG gli-colipid + phosphatidic acid
GM1	—	—	—
GM2	—	—	—
GM3	—	—	—
GD1a	—	—	—
GD1b	—	—	—
GD3	—	—	—
GT1b	—	—	—
GQ1b	—	—	—
Gal-C	—	+	—
GalNAc-GD1a	—	—	—
GD1a/GD1b	—	—	—

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Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflict of interest.

Statement of human rights For this case report, formal consent is not required.

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