Case Report / Olgu Sunumu

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Guillain-Barre Syndrome in a Patient with Primary Extranodal Intestinal Non-Hodgkin's Lymphoma: Paraneoplastic, Drug Induced or Coincidental?

Primer Ekstranodal İntestinal Lenfomalı Bir Hastada Gözlenen Guillain Barré Sendromu: Paraneoplastik Kökenli mi, İlaç Yan Etkisi mi, Rastlantısal mı?

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ABSTRACT

Neurological involvement is observed in 5%-25% of patients with lymphoma being either the first presentation of the disease or emerging during its course. However, Guillain-Barré syndrome is rarely reported. In this article, we present a case with intestinal lymphoma developing Guillain-Barré syndrome during the course of the disease. A 66-year-old male patient with primary extranodal intestinal lymphoma developed quadriparesis, sensory deficits and autonomic dysfunction while receiving chemotherapy. The findings of clinical, electrophysiological and laboratory examinations were consistent with Guillain-Barré syndrome. Guillain-Barré syndrome can potentially be fatal and mimic chemotherapy-induced neurotoxicity, especially in patients with lymphoma, and therefore, must be considered in the differential diagnosis. *(Archives of Neuropsychiatry 2014; 51: 288-292)*

Key words: Guillain-Barré syndrome, lymphoma, paraneoplastic syndrome, neurotoxicity, vincristine

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ÖZET

Lenfomalı hastaların %5-%25'inde nörolojik tutulum gerek ilk klinik prezentasyon olarak, gerekse hastalık seyri sırasında gözlenebilir. Ancak Guillain Barré sendromu nadiren bidirilmiştir. Bu yazıda intestinal lenfoma seyrinde gelişen bir Guillain Barré sendromu olgusu sunulmuştur. Bilinen primer ekstranodal intestinal lenfoması olan ve kemoterapi alan 66 yaşında bir erkek hastada subakut kuadriparezi, duyu bozukluğu ve otonomik disfonksiyon gelişmiştir. Klinik muayene, elektrofizyolojik incelemeler ve laboratuar bulgularının Guillain-Barré sendromu ile uyumlu olduğu saptanmıştır. Guillain-Barré sendromu ölümcül bir hastalık olma potansiyeline sahiptir ve özellikle lenfoma hastalarında kullanılan kemoterapötik ajanların nörotoksik yan etkilerini taklit edebilir, bu nedenle ayırıcı tanıda gözetilmesi ve tedavisinin hızla başlatılması önemlidir. *(Nöropsikiyatri Arşivi 2014; 51: 288-292)*

Anahtar kelimeler: Guillain-Barré sendromu, lenfoma, paraneoplastik sendrom, nörotoksisite, vinkristin

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Guillain-Barré syndrome (GBS) is an acquired acute neuropathy and covers the spectrum of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher syndrome, acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN) and acute pandysautonomia. GBS can affect both peripheral and cranial nerves and generally has a rapid progressive course with ascending paresis of the limbs and reduction or absence of reflexes. It is assumed that activation of T cells results in antibody production against protein antigens on peripheral nerves causing their damage. Viral and bacterial agents (especially campylobacter jejuni), immunisation, surgical treatments, drugs and neoplastic diseases are considered in the aetiology (1,2). Neurological involvement is observed in 5-25% of patients with lymphoma being either the first presentation of the disease or emerging during its course (3,4).

In this short report, we present a patient with primary extranodal non-Hodgkin's lymphoma (NHL) of the colon who developed GBS during the disease course.

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Case Report

A 66-year-old male patient presented with abdominal pain and loss of weight. He was examined due to similar complaints in another centre in September 2007. Computed tomography (CT) of the abdomen revealed thickening of the cecal wall and lymphadenomegaly in the peripheral mesenteries. Colonoscopy had shown a giant ulcerated mass lesion located in the distal part of the terminal ileum and cecum. The patient underwent a right hemicolectomy (Figure 1A). Histological examination of the mass showed a tumour containing high-grade atypical cells (Figure 1B) which were CD20 (+), LCA (+), CD3 (-) and cytokeratin (-). The patient was diagnosed with ileocecal large B-cell lymphoma and treated with 5 cycles of adjuvant chemotherapy including cyclophosphamide 750 mg/m^2 day 1, epirubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 (max 2 mg) day 1, prednisone 100 mg/m^2 day 1-5 (CEOP) every three weeks. After the 5th cycle of therapy, the patient refused treatment and had not been followed up further.

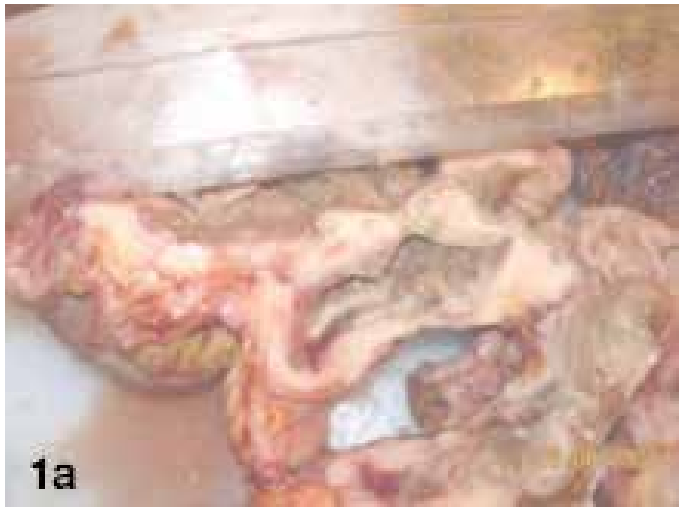

Figure 1A. Tissue consisting of small intestine and cecum which form a conglomerate with the grey yellowish tumour. The cross-section shows that all layers of the intestines are fused with each other and that thickness of the intestinal wall reaches 4 cm in some areas

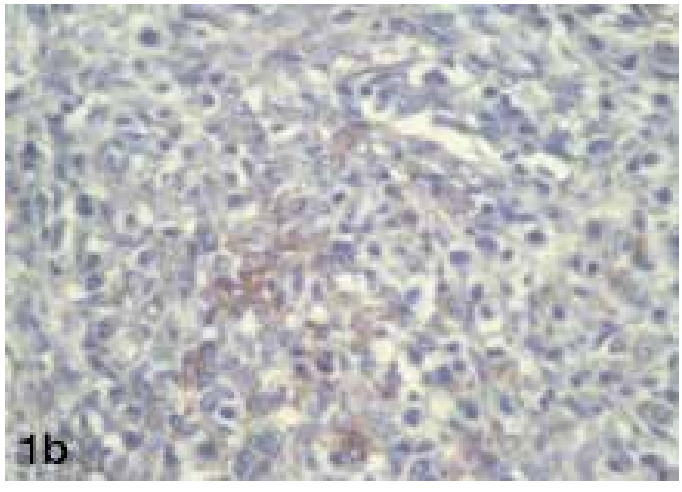

Figure 1B. Immunhistochemical staining (x40): Tumour cells showing diffuse dissemination in the intestinal tissue. The atypical cells are large, pleomorphic and CD20 (+), with vesicular hyperchromatic nuclei having distinct nucleoli

The patient was seen in our outpatient clinic in July 2008. Positron Emission Tomography/Computed Tomography (PET/CT) scanning revealed increased fluorodeoxyglucose (FDG) uptake in the area of the terminal ileum and adjacent conglomerated enlarged lymph nodes. The patient was diagnosed with a regional relapse and a new combination chemotherapy including cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 (max 2 mg) day 1, prednisone 100 mg/m^2 day 1-5, rituximab 375 mg/m^2 day 0 (R-CHOP), every tree weeks, was initiated.

Seven weeks after starting chemotherapy, the patient complained of severe fatigue, weakness in both limbs and difficulty in walking. He was normothermic (36.8 °C), slightly tachycardic (heart rate: 100/min), mildly hypertensive (blood pressure: 170/100 mmHg) and had a slight orthostatic hypotension.

The neurological examination revealed unaffected cranial nerves, symmetrical severe paresis of the lower limbs (muscle strength 3/5 according to the medical research council [MRC] grading system in the proximal muscles, and 2/5 in the distal muscles) and symmetrical slight paresis of upper distal muscles (muscle strength +4/5). Deep tendon reflexes were completely absent, there was no Babinski reflex or any other pyramidal sign. Sense of touch was reduced in both lower limbs up to the level of the knee. Sense of vibration was completely lost at the distal parts of the lower limbs. Cerebrospinal fluid (CSF) examination showed slightly elevated protein level (59 mg/dl) and no cells. Anti-GQ1a, anti-GQ1b and anti-GM antibodies were negative. In addition, protein electrophoresis and serum IgG were within normal ranges. Viral serology of serum and CSF was levels also negative. Magnetic resonance imaging (MRI) of the cranium and spinal cord was normal. Nerve conduction studies and needle electromyography (EMG) showed an acquired demyelinating polyneuropathy (PNP) which was accompanied by axonal loss. A decrease in compound muscle action potentials, prolongation of distal motor latencies and a reduction in motor conduction velocities were observed. Sensory action potentials were completely absent, median, ulnar and tibial F waves could not be obtained and needle electromyography showed signs of early denervation (Table 1a and 1b).

The patient was diagnosed with GBS, and intravenous immunoglobulin (IVIG) was administered at doses of 0.4 g/kg/day for 5 consecutive days. On the first day of treatment, the patient developed respiratory insufficiency due to respiratory muscle weakness and, oxygen saturation dropped to 80%. He was transferred to the intensive care unit (ICU) and he recovered on day 3. The treatment was completed in the ICU. A slight improvement of motor functions in the lower limbs was observed on examination but there was no change in deep sensation. Four weeks after initiation of treatment, muscle strength in distal limbs improved slightly, and sensation of vibration was weakly detected. Unfortunately, 2 months later, the patient died due to progression and complications of lymphoma.

Discussion

The pathophysiological relationship between GBS and cancer is not established yet, but a mechanism of paraneoplastic origin is blamed (5). Antibodies developing against tumour cell antigens are supposed to cause damage of the peripheral nerves due to molecular mimicry. However, this theory is losing ground if there are no antibodies found in the CSF and sera of patients, which is the case in approximately 30% (4,6). Neoplastic diseases also suppress or modulate the immune system, and thereby can lead to GBS, considering the occurrence of GBS after surgery, infections, transplantation or HIV infections all causing immune suppression to various degrees (4).

To date, approximately 25 cases of GBS occurring together with lymphoma in adults have been published. Approximately 65% of these cases are NHL, whereas 35% are Hodgkin's lymphoma. In Table 2, we summarized the characteristics of patients with GBS and lymphoma published more recently, between 2000 and 2012 (2 [index case], 7,8,9,10,11,12,13,14,15,16,17,18,19). To our knowledge, an association between GBS and primary extranodal intestinal lymphoma is not reported yet.

The underlying cause of neurological involvement during lymphoma is mostly neurotoxicity due to chemotherapeutic agents or direct invasion of peripheral nerves and nerve roots by tumour cells. The side effect of vincristine constitutes the major cause for peripheral neuropathy (9,20,21), although cytosine arabinoside and rituximab are also accused (10,11,14,15). The clinical spectrum can vary from mild paresthesia to serious quadriplegia.

In our case, there was an acute onset of symmetrical sensorimotor PNP starting in the distal parts and spreading proximally over days. Arterial hypertension, tachycardia and orthostatic hypotension were also observed and indicated involvement of the autonomic nervous system. Symptoms of the patient started approximately 7 weeks after the initial dose of chemotherapy. It could be assumed that the neurotoxic effect of vincristine was the cause. The cumulative dose of vincristine in our case was 4 mg, however, vincristine neuropathy occurs rarely at doses of 1.4 mg/m^2, unless there is an underlying disease, such as diabetic PNP, Charcot-Marie-Tooth disease or HIV infection (20,21). In these cases, severe neuropathies can be observed at even much lower doses. Additionally, vincristine is known to cause a predominantly axonal PNP (22), whereas in our case

Table 1a. Electrodiagnostic findings/Motor Nerve Conduction Studies

Nerve	Site of stimulation	Recording site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
L. Median	Wrist	APB	4.95	2.80	
	Elbow	APB	10.00	2.40	45.50
	Upper elbow	APB	13,15	2,30	54.00
L.Ulnar	Wrist	ADM	4.60	3.70	
	Lower elbow	ADM	6.50	3.50	57.90
	Upper elbow	ADM	10.65	2.90	38.60
	Axilla	ADM	12.45	2.60	66.70
L.Common Peroneal	Ankle	EDB	9.50	0.20	
	Fibular head	EDB	18.65	0.20	36.10
	Knee	EDB	21.40	0.20	35.50
R.Common Peroneal	Ankle	EDB	9.20	0.20	
	Fibular head	EDB	17.80	0.10	40.70
	Knee	EDB	21.20	0.00	23.50
L Tibial	Ankle	AH	7.30	0.30	
	Knee	AH	22.40	0.20	25.80
R. Tibial	Ankle	AH	7.20	0.40	
	Knee	AH	23.50	0.40	22.10

L.: left, R.: right, ms: millisecond, mV: millivolt, m/s: meter/second, APB: abductor pollicis brevis, ADM: abductor digiti minimi, EDB: extensor digitorum brevis, AH: abductor hallucis

Table 1b. Electrodiagnostic findings/Electromyography

	Spontaneous					MUAP			Recruitment
	IA	Fib.	PSW	Fasc.	HF	Amp.	Dur.	PPP	Pattern
L. Tib. Ant.	1+	None	None	None	None	-	-	-	No activity
L. Gastrocn. (med)	1+	None	None	None	None	-	-	-	No activity
R. Tib. Ant.	2+	2+	2+	None	None	-	-	-	No activity
L. First D. Inteross.	1+	1+	1+	None	None	1+	1+	1+	Discrete

MUAP: motor unit action potential, IA: insertion activity, Fib.: fibrillation potential, PSW: positive sharp wave, Fasc.: fasciculation, HF: high frequency, Amp.: amplitude, Dur: duration, PPP: polyphasic MUAP, L.: left, R.: right, Tib. Ant.: tibialis anterior, Gastrocn.: gastrocnemicus, First D. Inteross.: first dorsal interosseous. N: Normal

Table 2. Cases of GBS developed during the course of various lymphomas reported in the last 12 years

Author, Year	n	Gender / Age	Type of Lymphoma	Type of GBS	CT Regimen	Neurologic Involvement	Protein CSF	EMG	Treatment
Machida, 2012	1	F/83	B Cell NHL	NR	R-CHOP	Motor + Sensorial	177 mg/dl	-	IVIG + CS's
Seffo, 2010	1	F /70	T cell NHL	NR	CHOP	Motor + Sensorial	81 mg/dl	+	NR
Bahl, 2010	1	M / 8	B cell NHL	AMSAN	CHOP	Motor + Autonomic	20 mg/dl	+	IVIG
Terenghi, 2007	1	M / 51	B cell NHL	NR	R-CHOP	Motor	72 mg/dl	+	IVIG+CS's
Carmona, 2006	1	M / 57	B cell NHL	AMSAN	R-CHOP	Motor + Sensorial	63 mg/dl	+	IVIG
Wanschitz, 2006	1	F / 36	Burkitt's Lymphoma	AMAN	CHOP	Motor	232 mg/dl	+	IVIG+PPh
Kivity, 2006	1	F / 78	B cell NHL	AMSAN	none	Motor + Sensorial	62 mg/dl	+	IVIG
Magne, 2005	1	M / 74	Burkitt's Lymphoma	NR	R-CHOP	Motor + Sensorial	72 mg/dl	+	IVIG+PPh +CS's
Powers, 2005	1	F / 53	B cell NHL	AIDP	R-CHOP	Motor + Sensorial	NR	+	IVIG + PPh
Vigliani, 2004	1	M /16	Hodgkin Lymphoma	NR	ABVD	Motor + Sensorial	110 mg/dl	-	none
Naidech, 2002	1	F / 42	T cell NHL	NR	CHOP	Motor	227 mg/dl	+	PPh
Rodriguez, 2002	1	M / 17	T cell NHL	NR	ARA-C	Motor + Sensorial	162 mg/dl	+	IVIG
Zuk, 2001	1	F / 59	Burkitt's Lymphoma	NR	CHOP	Motor + Sensorial	24 mg/dl	+	none
Re, 2000	1	F / 21	T cell NHL	AIDP	GMALL	Motor + Sensorial	53 mg/dl	+	IVIG+PPh

n: number of patients, M: male, F: female, NHL: non-Hodgkin lymphoma, IVIG: intravenous immunoglobulin, PPh: plasmapheresis, CS: corticosteroid, AMAN: acute motor axonal neuropathy, AMSAN: acute motor and sensorial axonal neuropathy, AIDP: acute inflammatory demyelinating polyneuropathy, CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, ARA-C: cytosine arabinoside, GMALL: daunorubicin, vincristine, L-Asparaginase and prednisolone, ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, NR: not reported

demyelination was definitely prominent, which further supported the diagnosis of GBS.

In our patient, tests for HIV were negative, he did not suffer from diabetes mellitus and the family history for hereditary neuropathies was negative. In addition, the electro-diagnostic findings, the slight elevation of protein in the CSF and the moderate response to IVIG were all supporting the diagnosis of GBS. Furthermore, there were no cells in the CSF, gadolinium-enhanced cranial and spinal MRI scans were unremarkable and the cancer was in remission when symptoms of GBS first developed. In conclusion, there was no reason to assume that peripheral nerves were infiltrated by tumour cells.

One other major aspect in the differential diagnosis of GBS is chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP may also accompany lymphoproliferative diseases, such as lymphomas or plasmocytomas. Some authors suggest that CIDP is the chronic form of GBS. It is generally assumed that the disease continues to progress for about 8 weeks (23). Although electrodiagnostic features and CSF findings resemble GBS, the very slow progression of symptoms, its chronic relapsing course, the finding of monoclonal gammopathy of undetermined significance (MGUS) in 40-50% of patients, and a good response to treatment with corticosteroids are making the differential diagnosis easier (24). In our case, the acute onset, rapid progression and recovery after 4 weeks was prominent. Additionally, there was no gammopathy either, thus, CDIP was excluded.

In conclusion, we think it is important to recognise the clinical picture as early as possible to establish the differential diagnosis and to initiate treatment rapidly. It must be kept in mind that this syndrome may have a fatal outcome or at least may lead to permanent disability.

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