

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY IN CHRONIC GRAFT-VERSUS-HOST DISEASE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Case report

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ABSTRACT - The chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an unusual but important complication of hematopoietic stem cell transplantation (HSCT) rarely reported to date. We describe a 17-year-old woman with a diagnosis of acute myeloid leukemia due to Fanconi's anemia who was submitted to allogeneic HSCT and developed CIDP as part of graft-versus-host disease. Investigation showed high cerebrospinal fluid protein; electrophysiological studies revealed sensory-motor demyelinating polyradiculoneuropathy; muscle and nerve biopsy were compatible with CIDP.

KEY WORDS: graft-versus-host disease, hematopoietic stem cell transplant, bone marrow transplantation, neuropathy, polyneuropathy.

Polirradiculoneuropatia desmielinizante inflamatória crônica na doença do enxerto contra o hospedeiro após transplante de células hematopoiéticas alogênicas: relato de caso

RESUMO - A polirradiculoneuropatia desmielinizante inflamatória crônica (CIDP) é uma incomum, porém, importante complicação do transplante de células hematopoiéticas (HSCT) raramente relatada até a data. Nós descrevemos uma mulher de 17 anos com diagnóstico de leucemia mielóide aguda por anemia de Fanconi que foi submetida à HSCT e desenvolveu CIDP como parte da doença do enxerto contra o hospedeiro. A investigação mostrou elevação na proteína no líquido; estudo eletrofisiológico revelando polirradiculoneuropatia desmielinizante sensitivo-motora; e biópsia de músculo e nervo compatível com CIDP.

PALAVRAS-CHAVE: doença do enxerto contra o hospedeiro, transplante de células hematopoiéticas, transplante de medula óssea, neuropatia, polineuropatia.

Hematopoietic stem cell transplantation (HSCT) has found a place in the treatment of a variety of haematological disorders, including lymphomas, leukemias and multiple myeloma¹. Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality in HSCT recipients. GVHD may occur in acute or chronic forms, with symptoms arising before or after the 100th day after transplantation^{2,3}. Chronic GVHD symptoms affect predominantly the skin, mucosae and liver, and are due to activation of donor immunological cells against host tissues²⁻⁴. Neu-

romuscular complications have rarely been reported after HSCT, including neuropathies (axonal neuropathy, brachial plexopathy and polyradiculoneuropathy), myopathies and dysfunction of the motor endplate^{1,5-8}. Peripheral neuropathy as a complication of tissue transplantation has not received as much attention as other neurological complications^{6,8}.

Although peripheral nervous system involvement in chronic GVHD is uncommon, we describe a patient that developed an acquired chronic sensory-motor inflammatory demyelinating polyradiculoneuropathy

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(CIDP) with increased cerebrospinal fluid (CSF) protein in a setting of otherwise stable chronic GVHD.

CASE

We present a 17-year-old woman with a pancytopenia that had been followed up for 7 years and, after gingival bleeding, received a diagnosis of acute myeloid leukemia (AML) due to Fanconi's anemia, in 2002. She underwent an allogeneic HLA-matched bone marrow transplant and developed symptoms of acute GVHD, and kidney toxicity caused by cyclosporin. Chronic, progressive, GVHD developed and was managed with prednisone. Eight months post-transplant she was diagnosis as having meningitis caused by *Haemophilus influenzae* and also complained of bilateral auditory impairment.

At 10 months after transplant she complained of sensory disturbance (stocking-glove pattern) and distal weakness, with progression to the upper limbs. In 30 days the patient developed a flaccid tetraparesis. On general physical examination, she had oral and palatal mucosae white ulcers and multiple hypochromic skin lesions. Neurological examination revealed bilateral hearing loss, diffuse muscle

atrophy and hypotonia, generalized pain on muscle palpation, muscle strength grade 3 (MRC scale) in proximal and distal limbs, absent deep tendon reflexes and bilateral flexor/plantar response. Pain, temperature, vibration, joint position sense, pinprick and light touch were impaired distally in the arms and legs. Examination of coordination and equilibrium was not possible. Muscle pain limited gait examination. Laboratory tests showed normal blood counts, normal serum potassium and creatine kinase, aspartate aminotransferase 76 U/L (normal <35 U/L), alanine aminotransferase 108 U/L (normal <35 U/L) and gamma-glutamyl transpeptidase 173 U/L (normal <30 U/L). Laboratory evaluation for HIV and cytomegalovirus (CMV) infections, viral hepatitis, paraproteinemias and autoimmune disorders was unremarkable except for positive antinuclear antibodies 1:160 (normal <140) with diffuse pattern. CSF analysis showed 12 leukocytes/mm³ with lymphocytic predominance, glucose 62 mg/dL, protein 250 mg/dL.

The initial nerve conduction studies (NCS) revealed a marked slow motor nerve conduction velocity with low compound muscle action potential amplitude at the upper limb. The sensory nerve action potentials were not de-

Table 1. Sensory and motor nerve conduction studies.

Nerve	Variable response	1 st study	2 nd study	Normal
R-Median S	Latency (ms)	NO	NO	< 3.5
	Amplitude (mV)	NO	NO	> 15
	CV (m/s)	NO	NO	> 49
R-Ulnar S	Latency (ms)	NO	NO	< 3.1
	Amplitude (mV)	NO	NO	> 15
	CV (m/s)	NO	NO	> 49
R-Sural	Latency (ms)	NO	NO	< 2.1
	Amplitude (mV)	NO	NO	> 12
	CV (m/s)	NO	NO	> 39
R-Median M	D-Latency (ms)	7.1	11.2	< 4.2
	D-Amplitude (mV)	4.8	2.0	> 5.0
	P-Amplitude (mV)	3.8	NO	> 5.0
	CV (m/s)	25.7	NO	> 50
	F-wave (ms)	NO	NO	< 31
R-Ulnar M	D-Latency (ms)	5.1	9.2	< 3.4
	D-Amplitude (mV)	3.2	3.6	> 5.0
	P-Amplitude (mV)	2.0	2.3	> 5.0
	CV (m/s)	17.8	12.8	> 50
	F-wave (ms)	NO	NO	< 32
R-Deep Peroneal	D-Latency (ms)	NO	NO	< 5.0
	D-Amplitude (mV)	NO	NO	> 5.0
	P-Amplitude (mV)	NO	NO	> 5.0
	CV (m/s)	NO	NO	> 40
	F-wave (ms)	NO	NO	< 41
R-Posterior Tibial	D-Latency (ms)	NO	NO	< 5.5
	D-Amplitude (mV)	NO	NO	> 5.0
	P-Amplitude (mV)	NO	NO	> 5.0
	CV (m/s)	NO	NO	> 40
	F-wave (ms)	NO	NO	< 43

R, right; S, sensory; M, motor; D, distal; P, proximal; CV, conduction velocity; NO, not obtained.

Table 2. Reports of patients with CIDP after HSCT.

Author	Age/Sex	Underlying disorder	Latency*	CSF protein	Treatment	Outcome
Adams et al. ⁵	5/F	MOP	4 years	NP	P+CS	Recovery
Amato et al. ⁶	31/M	CML	6 months	NP	PSL+AZP+CS+Ivlg	Recovery
	44/M	CML	8 months	↑	PP+PSL+CS	Recovery
	29/M	AA	2 weeks	NP	PSL+CS+Ivlg	Recovery
	43/M	NHL	1 month	↑	PP+PSL	Recovery
Griggs et al. ¹⁰	42/M	NHL	3 years	↑	PP	Recovery
Nagashima et al. ⁷	32/M	NHL	5 years	NL	MPS	Partial recovery
Openshaw et al. ¹¹	36/M	CML	7 days	↑	P+CP+PP+Ivlg	Death
	21/M	HL	16 days	↑	P+CP+PP+Ivlg	Death
Peter et al. ¹	62/M	MM	1 month	NP	NP	Recovery
Present case	17/F	AML	10 months	↑	Ivlg+PP+P+MM	Recovery

*Interval after hematopoietic stem cell transplantation; M, male; F, female; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; AA, aplastic anemia; NHL, non-Hodgkin lymphoma; MOP, malignant osteopetrosis; MM, multiple myeloma; AML, acute myeloid leukemia; ↑, increased; NP, not performed; NL, normal; P, prednisone; CP, cyclophosphamide; PP, plasmapheresis; PSL, prednisolone; AZP, azathioprin; CS, cyclosporine; Ivlg, intravenous immunoglobulin; MPS, methylprednisolone; MM, mofetil mycophenolate.

tected in the right median, ulnar and sural nerves (Table 1). Needle electromyography (NE) showed diminished recruitment pattern in first dorsal interosseus, extensor digitorum communis, biceps brachialis, tibialis anterior and quadriceps femoris muscles. This electrophysiological pattern is indicative of a sensory-motor demyelinating polyradiculoneuropathy, consistent with CIDP (Table 1).

The patient received intravenous immunoglobulin (400 mg/kg for 5 days) with partial recovery, following to eight sessions of plasmapheresis with recovery. Clinical improvement occurred, and at discharge the patient was able to leave the hospital walking without help.

She was admitted again 12 months after HSCT with reduced strength associated with calf pain. CFS analysis showed 3.3 leukocytes/mm³, glucose 47 mg/dL, protein 430 mg/dL. Sorological reactions for CMV, IgM toxoplasmosis, VDRL test and PCR for herpes virus (HSV) were negative. The second electrophysiological study showed a worsened motor NCS, including conduction block, and NE findings, confirming the diagnosis of CIDP (Table 1).

She had a sural nerve and gastrocnemius muscle biopsies frozen in liquid nitrogen, cut in a cryostat and stained histologically and histochemically according to standard procedures⁹. The nerve biopsy had mild inflammatory perivascular lymphomononuclear infiltration in the endoneurium and epineurium, a reduction in the number of large myelinated fibers in some sectors of the fascicles, asymmetrical axonal degeneration within fascicles, occasional presence of myelin ovoid, and compact and disarranged myelin sheath in most of the material. The muscle biopsy had inflammatory perivascular lymphomononuclear infiltrate with invasion of the media. The inflammatory reaction spread from infiltrated vessels to adjacent muscle fibers and some had necrosis with phagocytosis.

With the diagnosis of CIDP (relapsing-remitting form) associated with GVHD after HSCT, the oral prednisone dose was increased to 1 mg/kg/day and mofetil mycophenolate was added. There was a substantial improvement in mus-

cle strength, besides the improvement in other manifestations of GVHD.

All studies were done following informed consent.

DISCUSSION

CIDP is an unusual but important complication of HSCT, rarely reported to date. To the best of our knowledge a consistent case of CIDP as a manifestation of GVHD was first reported in 1991 and was followed by other eight cases in the following decade, but CIDP after HSCT by AML had not been described (Table 2)^{5-8,10,11}. The case reported has neurological examination as well as laboratorial analysis, electrophysiological studies and histopathological examination compatible with 'CIDP' (relapsing-remitting form)¹²⁻¹⁴.

CIDP is a clinical syndrome based on a physiological and pathological concept as followed: (1) clinical features of chronic progressive or relapsing and remitting, symmetrical, sensory and motor polyradiculoneuropathy causing weakness of proximal and distal muscles; (2) CSF protein concentration is almost always increased; (3) electrophysiological evidence of demyelination is required for the diagnosis, but axonal degeneration can occur in evolution; (4) histological examination reveals demyelination with variable inflammatory infiltrates¹²⁻¹⁴. In addition to this core clinical picture, pure motor, pure sensory, multifocal sensory and motor and multifocal motor forms have been described as subcategories or separate entities^{12,13}. Also, the CIDP after HSCT can occur as a chronic progressive or relapsing and remitting CIDP^{6,7}.

Increased spinal fluid protein occurs in at least 90% of patients with CIDP¹³. Therefore, increased protein levels can be used as a supportive but not mandatory criterion for the diagnosis¹³. Increased CSF protein without pleocytosis is usually present in patients with peripheral neuropathy associated with chronic GVHD^{6,15}. Of the published CSF analyses, there was no evidence of blood-brain barrier disruption with increased CSF protein from chronic myeloid leukemia patients studied during HSCT and chronic GVHD, but there is report of increased CSF protein secondary to CIDP after HSCT (Table 2)^{6,7,10,11,16}.

The diagnosis of CIDP associated with chronic GVHD may require histological confirmation, which can be obtained in nerve biopsy specimens. The characteristic lesions of CIDP consist of patchy regions of demyelination and edema with variable inflammatory infiltrates¹⁴. The inflammatory infiltrate are found in both the endoneurium and the epineurium but, in contrast to vasculitic neuropathy, are more abundant in the endoneurium¹². The histological analysis of the nerve can show perivascular inflammatory cells in 54.5% of the patients with CIDP¹⁷. The inflammatory reaction in the endoneurial infiltrates is made of mononuclear cells, mainly lymphocytes and macrophages cells^{12,14}. In long stand disease is reported chronic inflammation in the perineurium and numerous onion bulbs in the endoneurium¹².

In this case, the nerve biopsy showed mild endoneurial inflammatory infiltrates, axonal alterations with asymmetric nerve fiber loss and reduction in the number of large myelinated axons compatible with CIDP, but onion bulbs not had been found probably due to short evolution time. The nerve ischemia secondary to inflammatory processes could induce acute axonal asymmetrical degeneration within the fascicle, that can occurs in CIDP, but had not been described to date in CIDP by chronic GVHD after HSCT^{15,18}.

There are a few studies about muscle biopsy pattern in CIDP with focus on the specific muscular abnormalities in this disorder. Nevertheless, we believe that specific muscle findings can be similar to nerve findings vary according to the time when the study is performed and the severity of the disease. Therefore, abnormalities as inflammatory perivascular infiltrate adjacent at muscle fibers can occur, as in our case.

The electrophysiological manifestation in chronic GVHD after HSCT may present as neuropathy (demyelinating and/or axonal neuropathy, sensory and/or motor neuropathy, multiplex mononeuropathy and polyneuropathy), myopathy and dysfunction of the

motor end-plate^{5,19-21}. The electrophysiological evidence of primary demyelination is required for the diagnosis of CIDP, according to strict diagnostic criteria, but as the disease advances, axonal degeneration becomes superimposed^{13,14}. The CIDP features associated with chronic GVHD can be found, but was not described previously associated with AML after HSCT⁶.

Neuropathies associated with GVHD had been reported^{2,4,6,7,10,21}. Temporary imbalances in the mechanisms of immune regulation, known to occur after immune reconstitution, have been suspected in the pathogenesis of post-transplantation neuropathies^{1,5}. Both cell-mediated and antibody-mediated immune responses to glycolipid or myelin protein antigens have been implicated in the pathogenesis of CIDP^{12,14}. It is interesting to note that when there is an immune-mediated alteration involved in these cases, patients normally shows an improvement with the resolution of the GVHD itself, as occurred in our patient^{2,6}. Until further studies are done, we can only speculate that the pathogenesis of the GVHD-associated CIDP can be related to the development of nerve demyelination and inflammation secondary to immune-mediated lesion.

The management of CIDP with corticosteroids, intravenous immunoglobulin and plasma exchange each provide short term benefit and immunosuppressive drugs possible may make long-term benefits¹²⁻¹⁴. Unfortunately, experience has been too limited to suggest specific regimens or the optimal sequence of immunosuppressant therapies in patients with CIDP associated with GVHD after HSCT.

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