Immune-mediated neuropathies after allogeneic hematopoietic stem cell transplantation: four case reports

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Background

Immune-mediated neuropathies (IMNs) have been reported as a rare (1%) and poorly understood complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), occurring in association with both acute or chronic graft versus host disease (a or cGVHD) as well as in the absence of GVHD. The clinical spectrum is extremely heterogeneous, ranging from more common inflammatory demyelinating neuropathies with acute or subacute-chronic course (i.e. Guillain-Barré syndrome or Chronic Inflammatory Demyelinating Polyneuropathy) to rarer axonal variants.

Case 1

Gender: M

Age: 59-year-old

Hematological history: allo-HSCT for acute myeloid leukaemia (AML). Autoimmune piastrinopenia 6 months after allo-HSCT

Neurological presentation: subacute onset of distal motor impairment at four limbs and paraesthesias in the hands 11 months after allo-HSCT

Nerve conduction studies (NCSs): predominantly axonal sensory-motor polyneuropathy (**Fig. 1**)

CSF analysis: mild increase of albumin (55 mg/dl, n.v. 10-30) and moderate barrier damage (blood-CSF albumin transfer 1.5%, n.v. <0.7%)

Therapy: intravenous immunoglobulins (IVIg) 0.4 mg/kg/day for 5 days; then intravenous 6-methylprednisolone (i.v. 6-MP) 1g/day for 5 days and 5 courses of plasma exchange (PEx)

Clinical course: initially severe worsening of distal motor impairment and appearance of both proximal weakness and sensory ataxia at four limbs. Then, after PEx, mild improvement of motor deficits of hands

Case 2

Gender: F

Age: 64-year-old

Hematological history: allo-HSCT for chronic myelomonocytic leukaemia type 2 (CMML-2). Acute GVHD (skin and bowel)

Neurological presentation: subacute onset of distal weakness and painful paraesthesias in the lower limbs (LL) approximately 8 months after allo-HSCT

NCSs: demyelinating changes at four limbs proximally and mild axonal sensory changes at LL (**Fig. 2**)

CSF analysis: only mild barrier damage (blood-CSF albumin transfer 0.9%)

Therapy: IVIg 0.4 mg/kg/day for 5 days

Clinical course: inconsistent clinical improvement and subsequent progressive worsening of neurological condition

Case 3

Gender: M

Age: 38-year-old

Hematological history: allo-HSCT for CMML-2

Neurological presentation: distal motor impairment and hypoesthesia in LL (especially on the right) 1 month after allo-HSCT

NCSs: axonal predominantly motor polyneuropathy (**Fig. 3**) and myopathic changes

CSF analysis: not performed because of patient's refusal

Therapy: not started because of patient's refusal

Clinical course: rapid worsening with increase of disability. Afterwards the patient has been lost at follow-up

Case 4

Gender: M

Age: 60-year-old

Hematological history: allo-HSCT for Diffuse large B-cell Non-Hodgkin Lymphoma (DLBCL). Acute GVHD (skin and bowel). Chronic GVHD (skin, bone, liver, muscle, piastrinopenia)

Neurological presentation: distal motor impairment in the left LL (steppage gait); then bilateral distal and proximal involvement a few months after allo-HSCT

NCSs: predominantly axonal sensory-motor polyneuropathy (**Fig. 4**) and myopathic changes

CSF analysis: only mild barrier damage (blood-CSF albumin transfer 0.8%)

Therapy: i.v. 6-MP

1g/day for 5 days

Clinical course: mild improvement of bilateral LL proximal weakness

	Motor					Sensory		
	CMAP (mV)	MCV (m/s)	DML (ms)	F wave latency (ms)		SAP (uV)	SCV (m/s)
ref	*>2*	*>40.6*	*<5.8*		*ref*	*>6*	*>42*
L Peroneus	0.1	33.9	22.05		***L Suralis***	0.63	36.4
ref	*>5*	*>41*	*<5.5*				
L Tibialis	1.3	34.9	5.80	69.85			
ref	*>5*	*>48*	*<3.3*		*ref*	*>6*	*>46*
R Ulnar	2.5	34.6	4.35	26.15	***R Ulnar***	6.9	35.6
ref	*>5*	*>46.8*	*<4*		*ref*	*>8*	*>46.8*
Median	NR	NR	NR		***Median***	NR	NR

Fig. 1

	Motor					Sensory		
	CMAP (mV)	MCV (m/s)	DML (ms)	F wave latency (ms)		SAP (uV)	SCV (m/s)
ref	*>2*	*>40.6*	*<5.8*		*ref*	*>6*	*>42*
L Peroneus	1.1	34.0	3.40		***R Suralis***	1.9	45.1
ref	*>5*	*>41*	*<5.5*				
L Tibialis	2.9	34.0	3.60	NR			
ref	*>5*	*>48*	*<3.3*		*ref*	*>6*	*>46*
Ulnar	NR	NR	NR	NR	***Ulnar***	NR	NR
ref	*>5*	*>46.8*	*<4*		*ref*	*>8*	*>46.8*
Median	NR	NR	NR		***Median***	NR	NR

Fig. 2

	Motor					Sensory		
	CMAP (mV)	MCV (m/s)	DML (ms)	F wave latency (ms)		SAP (uV)	SCV (m/s)
ref	*>2*	*>40.6*	*<5.8*		*ref*	*>6*	*>42*
L Peroneus	0.7	58.8	4.25		***L Suralis***	3.1	41.3
ref	*>5*	*>41*	*<5.5*				
R Tibialis	4.1	38.4	4.40	56.60			
ref	*>5*	*>48*	*<3.3*		*ref*	*>6*	*>46*
Ulnar	NR	NR	NR	NR	***Ulnar***	NR	NR
ref	*>5*	*>46.8*	*<4*		*ref*	*>8*	*>46.8*
R Median	4.5	52.2	3.6		***R Median***	11.9	41.7

Fig. 3

	Motor					Sensory		
	CMAP (mV)	MCV (m/s)	DML (ms)	F wave latency (ms)		SAP (uV)	SCV (m/s)
ref	*>2*	*>40.6*	*<5.8*		*ref*	*>6*	*>42*
R Peroneus	NE	NE	NE		***R Suralis***	1.1	35.2
ref	*>5*	*>41*	*<5.5*				
R Tibialis	0.1	29.2	6.15	NR			
ref	*>5*	*>48*	*<3.3*		*ref*	*>6*	*>46*
R Ulnar	3.3	61.9	2.8	NR	***R Ulnar***	19.4	40.4
ref	*>5*	*>46.8*	*<4*		*ref*	*>8*	*>46.8*
Median	NR	NR	NR		***Median***	NR	NR

Fig. 4

Discussion and conclusions

IMNs may occur after allo-HSCT ranging from demyelinating variants to rarer axonal forms. In our small case series, 3/4 patients presented with a severe axonal damage and although only in 2/4 patients definite manifestations of GVHD were observed (i.e. aGVHD in *Case 2*; a and cGVHD in *Case 4*), in all cases the generation of clonally expanded T-cells or of a humoral immune response against peripheral nervous tissue has been hypothesized as the causative mechanism. None of our patients had acute drug-induced neurotoxicity. Therefore, different immunotherapies (high-dose i.v. 6-MP, IVIg, PEx) were tried but only poor clinical response with subsequent relapsing or chronic progressive course was observed probably because of severe axonal damage in most of them.

In our experience we think that a baseline neurological examination before allo-HSCT encompassing NCSs should be established in clinical practice for the best assessment of possible subsequent PNS complications. Notwithstanding this small case series, our report suggests that peripheral neuropathy may represent a life-disabling and poor treatment-responsive complication of allo-HSCT.

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