

# Plasma exchange treatment of peripheral neuropathy associated with plasma cell dyscrasia

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**SUMMARY** Plasma exchange was used to treat 10 patients with polyneuropathy and a monoclonal antibody (plasma cell dyscrasia). Six patients had improvement of the neuropathy, while three patients had stabilisation of the neuropathy during plasma exchange. The patients who improved maintained a 64% or greater decrease in the monoclonal antibody between exchanges. Patients with axonal polyneuropathy as well as patients with demyelinating polyneuropathy recovered some neurologic function. With cessation of plasma exchanges, the monoclonal antibody titre approached pre-treatment levels and the neuropathy progressed. Plasma exchange was effective in rapidly lowering the level of monoclonal antibody and allowing for some recovery of neurologic function.

Chronic progressive polyneuropathy has been reported in 8% of patients with Waldenström's macroglobulinaemia,<sup>1</sup> 39% of those with multiple myeloma,<sup>2</sup> and in many patients with monoclonal immunoglobulins (plasma cell dyscrasias) without other evidence of a malignant disease.<sup>3-6</sup> Several observations suggest that the monoclonal antibody found in these patients may cause the neuropathy: (1) monoclonal antibody may be demonstrated in the sural nerve biopsy,<sup>7,8</sup> (2) some of these monoclonal immunoglobulins have a cross-reacting idiotype suggesting recognition of a common antigenic determinant,<sup>9</sup> (3) the monoclonal antibody can be absorbed from the serum by incubation with peripheral nerve components,<sup>10,11</sup> (4) a neuropathy in mice can be produced by passive transfer of these monoclonal antibodies,<sup>12</sup> and (5) suppression of the plasma cell dyscrasia with chlorambucil, steroids, or radiotherapy has been accompanied by improvement of the neuropathy.<sup>13-15</sup> If the monoclonal antibody does bind a nerve component to perpetuate

the neuropathy, reduction in the level of antibody should stabilise the neuropathy or permit recovery of nerve function. We therefore studied the response of the neuropathy to plasma exchange.

## Material and methods

### *Patient characteristics*

Between October 1978 and June 1982, of approximately 220 patients with peripheral neuropathy admitted to the Neurological Institute of Columbia Presbyterian Medical Center, 10 were found to have a monoclonal antibody. The 10 patients (table 1), five men and five women, were between the ages of 32 and 72 years. Four patients had equally severe motor and sensory symptoms; two had a predominantly motor disorder, and four had predominantly or solely sensory neuropathy. Four patients also had skin involvement with areas of epidermolysis with or without nodules. In these cases, the monoclonal immunoglobulin was shown to be deposited in the dermis by direct immunoperoxidase or immunofluorescent studies.

Seven of the 10 patients had normal bone marrow examinations and were classified as plasma cell dyscrasias of unknown significance. Three cases had a malignant lymphoproliferative process: Case 2 had myeloma with osteolytic lesions of the skull; Case 4 had osteosclerotic myeloma; and Case 6 had a poorly differentiated lymphocytic lymphoma with marrow involvement. Immunoglobulins were evaluated as described below. Six of the 10 paraproteins were of the IgM class and four were of IgG class with concentrations of 200 to 1700 mg/dl. The IgG of Case 2 and the IgM of Case 6 precipitated on cooling the serum to 4°C.

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Table 1 Clinical characteristics

Case	Sex/Age	DoS	Predominant nerve symptom motor (m) sensory (s)	Nerve pathology	Skin lesions	Other diagnoses	Paraprotein	
							M-Ig	Concentration (mg/dl)
1	M/52	36	m/s	dm*	—	—	Gk	200
2	F/55	29	m/s	ax†	+	myeloma	G	— (c)
3	M/72	18	m/s	?	—	—	Gk	1700
4	M/32	10	m	ax	—	myeloma (osteosclerotic)	Gλ	700
5	F/58	16	s	ax	—	—	Mk	550
6	F/67	8	m/s	ND‡	—	lymphoma	Mk	600 (c)
7	M/45	132	m	dm	—	—	Mk	390
8	F/53	30	s	ax	+	—	Mk	1150
9	F/58	28	s	ax	+	—	Mk	1150
10	M/62	60	s	ax	+	—	Mk	1200

\*dm = demyelinating polyneuropathy as the predominant feature of teased fibre preparation of a sural nerve biopsy.

†ax = axonal changes as the predominant feature of teased fibre preparation of sural nerve biopsy specimen.

? predominant pathologic feature of teased fibre preparation of sural nerve uncertain.

‡ND = no biopsy specimen.

(c) denotes cryoglobulin.

DoS = Duration of symptoms prior to plasmapheresis (in months).

### Immunoglobulin studies

The monoclonal antibody was detected by cellulose acetate electrophoresis in 0.25 M barbital buffer pH 8.4 and characterised by immunoelectrophoresis in 0.5% highly purified agarose gel (Marine Colloids, Rockland, Me) in 0.05 M barbital buffer pH 8.4 using antisera specific for  $\gamma$ ,  $\alpha$ ,  $\mu$ ,  $\lambda$ , and  $\kappa$  immunoglobulin determinants. A cryoprecipitable antibody was sought by clotting the serum specimen at 37°C, decanting the serum and refrigerating the serum at 4°C for up to 72 hours. If a cryoprecipitate appeared, the serum was centrifuged at 1000 rpm at 4°C for 10 minutes (International Equipment Co, Needham Hts, Ma), the cryoprecipitate redissolved in 1/5 the starting volume in 0.15 M NaCl with 0.01 M phosphate buffer pH 7.4 at 37°C, and evaluated as above. Immunoglobulins were quantified by a fluorescent immunoassay (International Diagnostic Technology, Santa Clara, Ca) at the start of each plasma exchange.

Nerve biopsy evaluations were performed as previously reported.<sup>16</sup>

### Plasma exchange

Exchanges were performed using a Haemonetics Model 30 Intermittent flow cell centrifuge (Haemonetics, Braintree, Ma). A 16 gauge needle was inserted in each antecubital vein. Twenty ml of 46.7% sodium citrate diluted in 500 ml of normal saline was the anticoagulant. One hundred ml of this solution was used for each litre of blood. Each litre of plasma removed was replaced with 250 ml of Ringer's lactate, 250 ml of 0.9% sodium chloride, and 250 mg of 0.004 M sodium coprylate, 0.004 M sodium acetyl tryptophonate containing 12.5 gm albumin (Plasmanate<sup>®</sup>, Travenol, Deerborn, Il). Blood volume (BV) was estimated as 70 mg/kg  $\times$  weight in kg. Plasma volume (PV) was calculated as  $PV = BV - (BV \times \text{haematocrit})$ . Two thousand to 2800 ml of plasma were removed during each session.

Prior to each plasma exchange, the patient was evaluated by one of the authors, either WHS or MRO, for change in the neuropathy. In an attempt to standardise the evaluation, the parameters evaluated included aspects of daily living, clinical measurements of extremity muscle

strength, sensory level to pinprick and vibration, and extremity reflexes.

The plasma exchange treatment was continued as long as the patient was stable or improving. All patients except Cases 1 and 5 were ultimately treated with chemotherapy. The plasma exchange therapy was discontinued after about 3 months of treatment and only resumed if there was clinical evidence of progression of the neuropathy.

*Case 1* In 1971 at the age of 51 years a Whipple procedure was performed for a gastric carcinoma. In 1976 he received the swine influenza vaccine. Four months later he noted the onset of paraesthesias which steadily progressed. By mid 1977, there was distal limb weakness and prednisone 50 mg every other day was started with little change in function. By March 1978, he could not walk. There was decreased sensation to pin and vibration below the knees and elbows, bilateral wrist drop, and weakness against resistance of small muscles of the hands, and weakness of the extensors and flexors of the ankles. The laboratory studies were significant for a small IgG paraprotein in the serum of 200 mg/dl, a cerebrospinal fluid protein of 321 mg/dl, and slow nerve conduction velocities. With an increase in the dosage of prednisone to 100 mg a day, there was marked improvement in the weakness. Over one month he regained some strength in the arms and legs and could now feed himself and walk with a four post walker. As the dosage of prednisone was slowly decreased to 50 mg every other day, the neuropathy progressed. By April 1979, he required short leg braces to walk. The gastrocnemius and anterior tibialis muscles were too weak to work against gravity. Deep tendon reflexes were absent, and there was decreased sensation to pin and vibration below the elbows and knees. Plasma exchanges were begun daily for 5 days. Two weeks later the anterior tibialis muscle was able to flex the ankle against gravity. This activity remained stable until 5 weeks after plasma exchange when the distal leg muscles were no longer functional against gravity. Regular plasma exchange for 5 days every 4–5 weeks was resumed, again with improvement in the strength of the anterior tibialis muscle within 2 weeks later.

Over the subsequent 2 years, the plasma exchanges were

Table 2 Plasma exchange results

Case	Other Rx	Frequency	Duration (wk)	% decrease monoclonal antibody*	Clinical change†		Earliest objective evidence of response‡ (wk)
					Pre plasma exchange trial	Post plasma exchange trial	
1	P	5 days every 5-8 weeks	139	75	Unable to walk or stand	Walks unaided, normal strength	1
2	M	3 in 1st wk, weekly for 8 wk, then every 2 wk.	131+	‡	Unable to climb stairs	Normal strength	2
3	—	3 times a week for 2 weeks, then weekly	4	66	Weakness of all muscles groups (3/5)	Normal strength	2
4	RT + P.	2 times a week	14	100	A. weakness of small muscles of hands (2/5) B. absent proprioception in feet	A. small muscles of hands (4/5) B. return of proprioception	2
5	—	8 of first 14 days, then weekly	8	64	Unable to walk or sit	Walks with a walker	2
6	—	daily for 5 days	2	—	Decreased proprioception and vibration, no motor weakness	Weakness of anterior tibialis and gastrocnemius	progression
7	C	weekly	12	70	Distal wrist extensor weakness against gravity	Able to extend wrist against gravity	1
8	C	weekly	10	68	Decreased distal superficial sensations	No change	—
9	C	weekly	12	32	"	"	—
10	—	2 consecutive days biweekly	6	0	"	"	—

P = prednisone  
M = melphalan  
RT = radiotherapy  
C = chlorambucil  
\* = Antibody titre measured 1 week after plasma exchange.  
† = Selected clinical parameter that best documents change in neurologic status. Post plasma exchange findings were obtained at the time of the last plasma exchange treatment. This varied from 2 weeks in Case 6 to 139 weeks in Case 1 reflecting the duration of plasma exchange therapy.  
‡ = Cryoglobulin disappeared in first 3 days of plasma exchange and did not return.  
§ = Clinical evaluations were performed prior to each plasma exchange.

continued for 5 days every 4-5 weeks. Four months after instituting plasma exchange, the dosage of prednisone was lowered to 30 mg every other day. At that time, he no longer wore leg braces. He could walk on his heels, but not his toes and muscle strength was normal. There was decreased sensation to pin, vibration and proprioception below the mid-forearm and mid-calf. One year later the dosage of prednisone had been decreased to 10 mg every other day. He could now walk on toes and heels. The sensory examination was unchanged, but the biceps and triceps reflexes had returned. The electrophysiologic studies documented the improved nerve function (table 3). He had the last plasma exchange in January 1982. In October 1982, the medication was 5 mg of prednisone on alternate days. The neurological examination was normal except for minimal glove and stocking hypoalgesia. The IgG paraprotein was present at 200 mg/dl.

Case 2 At age 36 years this woman was hospitalised for cervico-lumbar arthritis and keratitis. At age 53 paraesthesiae developed in the toes along with blisters of the fingers and toes followed by progressive weakness. By age

55 she could no longer work zippers or buttons. Pain and touch sensation were impaired below the elbows and knees, along with decreased proprioception. There was weakness of the small muscles of the hands to resistance and inability to stand on the toes. Deep tendon reflexes were absent. The haemogram was normal. The serum contained a small amount of IgG monoclonal immunoglobulin which behaved as a cryoglobulin. A sural nerve biopsy showed an axonal neuropathy with no evidence of amyloid. Skin biopsy revealed interdermal deposition of IgG but no amyloid. The skeletal radiographs showed small osteolytic lesions of the skull. On biopsy the lytic lesion contained sheets of plasma cells. On September 9 plasma exchange was begun for 3 days then weekly thereafter. Melphalan, 8 mg/d for 10 days was begun on September 12 and decreased to 2 mg/d on September 23. Within 1 week of the onset of plasma exchange the skin lesions cleared and the cryoglobulin was no longer present in the serum. Two weeks after the onset of plasma exchange walking improved and she was again able to perform fine manipulations. By October 20, the gait was normal and she was able

Table 3 Results of electrophysiologic studies in case 1

Nerve	Time from onset of plasma exchange therapy (months)										
	Month	0		4	11	13	23	23		23	
		V	A					V	A		
Median motor		14.9	0.45	12.6	—	10	1	15.1	0.95	14.4	4.8
Median sensory		NR	—	NR	—	NR	—	NR	—	NR	—
Peroneal Motor		NR	—	NR	—	NR	—	10.7	0.8	9.4	2
Sural sensory		NR	—	NR	—	NR	—	NR	—	9.5	0.4

V = Velocity in m/s.  
A = Amplitude in mV.

to climb stairs. There was no evident muscle weakness. Impaired sensation was now present below the mid-palms and ankles with impaired proprioception at the toes.

After 2 more weekly treatments of exchanges, the procedures were stopped and 20 mg per day of prednisone added. Ten days later the paraesthesiae had worsened. Sixteen days after stopping plasma exchanges, despite melphalan and prednisone the sensory impairment had progressed to the knees and mid-forearm, along with recurrence of weakness of the anterior tibialis muscle and small muscles of the hands. The IgG cryoglobulin was now evident. Plasma exchange was restarted. The sensory and motor findings improved, but proprioception remained impaired below the ankles. She is continuing plasma exchange every 2 weeks, 34 months after the onset of therapy. If the plasma exchanges are delayed to 3 week intervals, the muscle weakness progresses along with decreasing sensation.

*Case 7* The patient has previously been reported.<sup>6</sup> Despite chlorambucil therapy, the neuropathy progressed between February and April with the loss of wrist extensor function. Plasma exchanges were begun. Two weeks after the initial plasma exchange, he was able to hold the wrists against gravity. A week later, the wrists could be extended against gravity. The plasma exchanges were interrupted for 16 days and the extensor activity of the wrists disappeared. With resumption of plasma exchanges the ability to extend the wrists against gravity returned within one week. The plasma exchanges were continued weekly for 3 months with return of full wrist extensor function and function of the anterior tibialis muscles to the extent he no longer required ankle braces. The plasma exchanges were discontinued after 3 months without a rebound of the monoclonal IgM due to effects of 6 months of chlorambucil therapy. The IgM spike continues to be suppressed and the muscle strength has improved to the extent that he is able to perform woodworking projects. There is still significant atrophy of the small muscles of the hands 3 years after the IgM spike has been eliminated. Cases 8 and 10 have been presented in detail.<sup>11</sup>

## Results

Five of the six patients received exchanges three or more times in the first week and demonstrated improvement in neurologic function (table 2), whereas only one of the patients plasma exchanged less frequently improved during plasma exchange. The post plasma exchange clinical results were obtained at the time of the last plasma exchange treatment. All four patients with IgG plasma cell dyscrasias (Cases 1-4) had neurological improvement, but only two of the six patients with IgM plasma cell dyscrasias improved. Five of the six patients with mixed motor and sensory symptoms or predominantly motor symptoms improved whereas only one of the four patients with almost exclusively sensory symptoms improved with plasma exchange. Both patients with demyelinating polyneuropathy improved with plasma exchange, but only four of the

six patients with axonal polyneuropathy by biopsy had objective improvement.

Electrophysiologic studies were obtained on patients who demonstrated clinical improvement except for Cases 2 and 5 who refused repeat studies. In Case 1 (table 3), the change in electrophysiologic parameters was not evident until 13 months after the onset of plasma exchange therapy despite marked improvement in the clinical status by 4 months after the onset of plasma exchange therapy. In the other cases, there was no change in the nerve conduction studies by the completion of the plasma exchange trial (1 to 3 months).

The effectiveness of plasma exchanges appeared to be independent of concomitant chemotherapy. As can be seen from the report of Case 1, disease progression occurred while taking prednisone, but the prednisone could be tapered and stopped after the plasma exchanges were begun with continuing clinical improvement. In Case 2, six weeks after the onset of chemotherapy and plasma exchanges there was marked clinical improvement and plasma exchanges were discontinued. The IgG cryoglobulin reappeared and despite the addition of prednisone, the paraesthesiae and weakness progressed. In Case 7, progressive paralysis of the extensors of the wrists developed during the first 2 months of chlorambucil therapy. The extensors of the wrists functioned weakly one week after starting plasma exchanges. When the plasma exchanges were interrupted for 2 weeks the IgM returned to 88% of the pre-pheresis level with loss of activity of the wrists. Wrist extensor activity recovered with resumption of plasma exchanges. Plasma exchange in Case 8 was not begun until after 4 months of slow progression of the sensory neuropathy on chlorambucil alone.<sup>11</sup> All patients who demonstrated clinical improvement in the neuropathy did so within 2 weeks of onset of plasma exchange.

There was an apparent relationship between the degree of suppression of the monoclonal immunoglobulin and clinical response. Five of the six patients who improved after plasma exchange had a 64% or greater decrease in the monoclonal immunoglobulin. In Case 2 the cryoglobulin disappeared within 3 days of the first plasma exchange and it did not recur while on plasma exchange therapy. The effectiveness of plasmapheresis is depicted in the figure. For a monoclonal IgM, the antibody titre was decreased by up to 70% at 24 hours after one plasma exchange but returned to pre-treatment levels within 3 weeks (fig, Case 7, 10). An IgG antibody was decreased by 40% at 24 hours after plasma exchange (fig, Case 1). After a week of daily plasma exchanges the monoclonal IgG was only 15% of the pre-exchange values, but

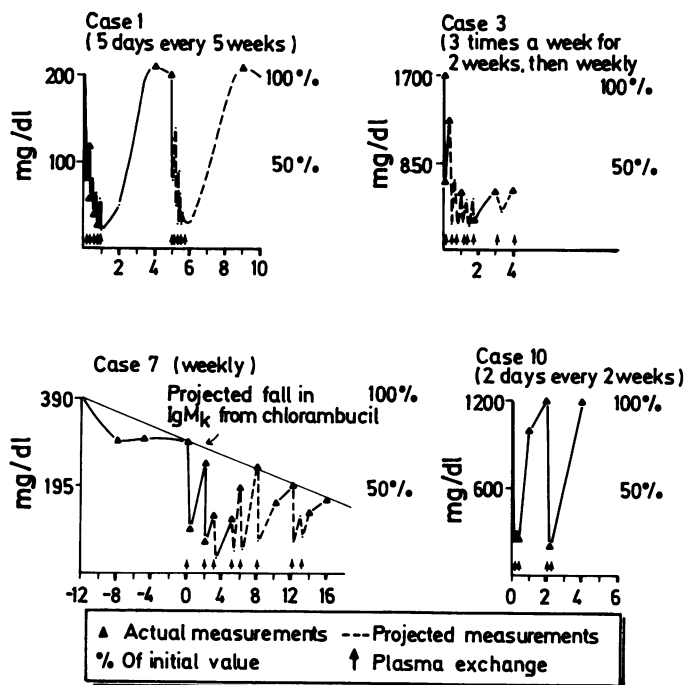


Fig Effect of plasmapheresis schedule on concentration of serum monoclonal immunoglobulin.

increased back to pre-exchange levels between the third and fourth weeks after stopping plasma exchange therapy. With weekly plasma exchange therapy (fig, Case 3) the monoclonal IgG levelled at about 30% of the pre-exchange level. In the patients with monoclonal (IgM antibodies, fig, Case 7, 10), the IgM antibody returned to pre-plasma exchange levels after 2 weeks of no therapy. As can be seen in Case 7, chemotherapy took 24 weeks to cause a 50% decrease in the level of the IgM, but a fall in the level of the antibody of this magnitude or greater occurred with one plasma exchange treatment. On weekly plasma exchange IgM levels reached a plateau after two to three treatments at 32 to 70% of the pre-treatment levels when measured just before the next plasma exchange. Daily plasma exchanges had no discernible effect on the IgM level after the first treatment (fig) whereas the IgG level plateaued at about 30% of pre-treatment levels after three plasma exchanges performed every other day.

When the regular plasma exchange treatments were interrupted, the areas of most recent neurological recovery relapsed first as the monoclonal antibody approached pre-pheresis levels. In the five patients treated with immunosuppressive drugs, it was not until the drugs suppressed the monoclonal antibody titre to 50% or less of the titre prior to

plasma exchange that the plasma exchange could be discontinued with continuing stabilisation or improvement in the neuropathy. This required at least 2 months of alkylating agent therapy.

**Discussion**

Progressive polyneuropathy associated with a plasma cell dyscrasia is not one entity but represents many different mechanisms of peripheral nerve injury. While it is presumed that the monoclonal antibody is capable of binding to a nerve component, this has only been demonstrated in three of the 10 patients in this study—Cases 7,<sup>10</sup> 9,<sup>11</sup> and 10.<sup>11</sup> Of these three patients, the IgM of Case 7 reacted with MAG and was associated with a demyelinating polyneuropathy, while in Cases 9 and 10 the IgM reacted with chondroitin sulphate and was associated with an axonal polyneuropathy. The other cases are being evaluated to see if the monoclonal antibody binds to other nerve components. It is likely that the nerve component to which the antibody binds, the degree of neural injury, and the kinetics of the class of antibody involved in this reaction are all important in the manifestations of the neuropathy and its potential for recovery.

If the antibody activity is related to the progressive neuropathy, plasma exchange should be a

reasonable therapeutic modality. One plasma exchange is capable of decreasing the IgM level at 24 hours by 70% or the IgG level at 24 hours by 40%. Weekly plasma exchange maintains suppression of the monoclonal antibody in the range of 30 to 70% of pre-treatment levels without adverse effects. More frequent plasma exchanges may suppress the antibody titre more.

Plasma exchange has been helpful in chronic dysimmune polyneuropathy.<sup>17,18</sup> Plasma exchange alone or with immunosuppressive therapy resulted in objective improvement of six of our 10 patients and the neuropathy seemed stable after previous progression in another three patients. Sodium citrate was the anticoagulant employed because the IgM in some patients with polyneuropathy interact with heparin.<sup>11,19,20</sup> Objective improvement was noted within 2 weeks of plasma exchange in the six patients who improved, an interval too short for the immunosuppressive drugs when used, to be effective.

In Case 1, after 34 months of therapy, the plasma exchanges were discontinued. Despite persistence of the IgG paraprotein at 200 mg/dl the neuropathy did not relapse. By contrast in Case 2 the plasma exchanges must continue even after 32 months of therapy or the neuropathy progresses. The lack of progression of the neuropathy in Case 1 despite persistence of the IgG paraprotein suggests that other factors besides the paraprotein level may be involved in this patient's polyneuropathy. Since we have not demonstrated that this antibody interacts with nerve, there could be another antibody whose level has decreased over 34 months. Another possibility is that the antigenic determinant is expressed on injured nerves and not on healthy nerves allowing the antibody to only perpetuate an existing neuropathy. This could also be why the recently improved nerves relapsed first when plasma exchange was interrupted. Case 1 is the only one in which the neuropathy stabilised after initial improvement without a persistent decrease in the level of the monoclonal antibody.

The lack of change in the electrophysiologic studies despite improvement in strength and function in patients who respond to plasma exchange may be a question of sensitivity of the two parameters. Improved strength reflects more proximal nerve function and may be magnified by reinnervation of a few muscle fibres. The electrophysiologic studies test more distal nerve function which takes longer to improve. As is documented in Case 1, functional improvement occurred quickly, but it took over 1 year before electrophysiologic improvement could be shown.

Although the long-term safety of plasma

exchange has not yet been proven, 800 ml plasma exchanges every 2 weeks without replacement proteins for 1 year has not been associated with an unusual incidence of infections, altered cellular immunity, or other untoward effects.<sup>21-23</sup> In our patients, total plasma exchange with albumin replacement weekly for over 2 years has not encountered untoward side effects.

Given the safety of plasma exchange and the rapidity of response in motor function, patients with rapidly progressive polyneuropathy and a plasma cell dyscrasia should have plasma exchanged three or more times in the first week. Subsequently, plasma exchange should be performed frequently enough to maintain the antibody titre at less than 40% of pre-treatment values. The frequency and duration of plasma exchange depends upon the clinical response, and the utilisation and effectiveness of immunosuppressive drugs to decrease the monoclonal antibody titre. Immunosuppressive drugs, however, have long term risks including the induction of malignancies.<sup>24,25</sup> Therefore, in patients without overt myeloma, lymphoma, or macroglobulinaemia risks of adding immunosuppressive drugs must be considered.

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