Restricted use of vγ genes in poems syndrome

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PThe POEMS syndrome is characterized by the association of polyneuropathy (P), organomegaly (O), endocrinopathy (E) and skin changes (S). These lesions are secondary to a plasma cell dycrasia which, in most patients, produces a monoclonal component (M).[1,2] The plasma cell dyscrasia in POEMS differs from multiple myeloma in that the light chains are of the λ type whereas the bone lesions are osteosclerotic and, strikingly the cure of the dyscrasia, if possible (solitary plasmacytoma), cures the other signs and symptoms. We investigated λlight chains because we found it intriguing that the λtype restriction of POEMS admits of no more than 1% exception.[1,2] In this study we determined the Igλ variable region sequences from 2 λ-chain producing POEMS syndrome by reverse-transcriptase polymerase chain reaction.

Material and methods.

The two patients with POEMS syndrome had demyelinating neuropathy, IgG? M component and a single osteolytic and sclerotic lesion in the iliac wing. One patient had diffuse skin thickening and the other gynaecomastia. Total RNA was prepared from plasmocytoma by the guanidium isothiocyanate/cesium chlorid method. Total RNA was used as a template for synthesizing single-stranded cDNA using reverse transcriptase and oligodeoxythymidylic acid primer. 5' primer matched the Vλ1-Vλ2-Vλ3 consensus leader region (5'-ATGGCCK-GSWYYSYTCTCCTC-3') and 3' primer matched the consensus upstream part of the cλ exons (5'-CTCC-CGGGTAGAGAAGTCACT-3'). Amplification of the cDNAs by PCR was performed and amino acid sequences were deduced from those of the complementary cDNA. To identify the presumed germline gene of monoclonal V regions, alignments, were sought for in IMGT (http://imgt.cines.fr). Analysis of the distribution of somatic mutations in each sequence was carried out by the method of Chang and Casali.[3]

Results and Discussion

The two ARN sequences had 89% identity. Both light chain genes belonged to the Vγ1 family. They derived from germline IGLV 40-01 also known as 1e with 93% (case 1) and 92% (case 2) identity with germ-line.[4] In case 1, the average mutation rates of FWR and CDR were 7.6% and 11.% respectively and 8.1% and 8.8% respectively in case 2. The CDR R/S ratio was 9 in case 1 and 2.5 in case 2 compared to an expected ratio of 2.98. Antigen driven selection was thus documented in case 1 (p=0.028) but not in case 2 (p=0.19). In framework regions, the R/S ratios were lower than expected in both case 1 and case 2 [0.75 (p=0.07) and 2.0 (p=0.02) respectively], for an expected value of 2.62. Three amino acid substitutions were found in both patients: substitution of Histidine +34: asparagine in CDR1, serine +52: asparagine in CDR2 and lysine+103 : glutamine in FWR4.

Discussion

Despite the small number of patients involved owing to the rarity of POEMS and to difficulties in collecting useful samples because of their localized nature, our

Table 1. Nucleotide sequence of the two patients in comparaison with germline IGLV1-40*01 or 1e (http://imgt.cines.fr).

1	2	3	4	5	6	7	8	9	11	12	13	14	15	16	17	18	19	20	21	22
AGA	TCT	GTG	CTG	ACG	CAG	CCG	CCC	TCG	GTG	TCT	GAG	GCC	CCA	GGG	CAG	AGG	GTC	ACC	ATC	TCC
CAG								A			G									
				CDR1																
23	24	25	26	27	28	29	30	31	32	33	34	35	39	40	41	42	43	44	45	46
TGT	ACT	GGG	ACC	GGC	TCC	AAC	ATC	GGG	GCA	GGT	TAT	GAT	GTA	AAT	TGG	TAT	CAG	CAG	TTT	CCA
C			G	A										C C		C			C	
								CDR2												
47	48	49	50	51	52	53	54	55	56	57	58	66	67	68	69	70	71	72	74	75
GGA	AGA	GCC	CCC	CGA	CTC	CTC	ATC	TAC	GCT	AAT	AAC	AAT	CGA	CCC	TCA	GGG	GTC	CCT	GAC	CGA
	C			AA				T	G	C	G		G							
76	77	78	79	80	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98
TTC	TCT	GGG	TCC	AAG	TCT	GGC	ACT	TCA	GGC	TCC	CTG	GCC	ATC	ACT	GGG	CTC	CAG	GCT	GAA	GAT
		C					C		C										G	
								CDR3												
99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114					
GAG	GCT	GAC	TAT	TAC	TGC	CAG	TCC	TAT	GAC	AGC	AGC	CTG	AGT	GGC	TGG					
		T												T	C					
1	2	3	4	5	6	7	8	9	11	12	13	14	15	16	17	18	19	20	21	22
CCA	GTC	GTG	CTG	GCG	CAG	CCG	CCC	TCA	GTG	TCT	GGG	GCC	CCA	GGG	CAG	AGG	GTC	ACC	ATC	TCC
AG	TCT			A																
				CDR1																
23	24	25	26	27	28	29	30	31	32	33	34	35	39	40	41	42	43	44	45	46
TGC	ACT	GGG	AGC	AAC	TCC	AAC	ATG	GGG	GCA	GGT	TAT	GGT	GTA	AAC	TGG	TAC	CAA	CAA	CTT	CCA
				G			C					A		C			G	G		
								CDR2												
47	48	49	50	51	52	53	54	55	56	57	58	66	67	68	69	70	71	72	74	75
GGG	GCA	GCC	CCC	AGA	CTC	CTC	ATC	TAT	GGT	AGC	AAC	ATT	CGG	CCC	TCA	GGG	GTC	CCT	GAC	CGA
A	A			A						A	G	A								
76	77	78	79	80	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98
TTC	TCT	GGC	TCC	AAG	TCT	GGC	ACC	TCA	GCC	TCC	CTG	GCC	ATC	ACT	GGC	CTC	CGG	GCT	GAG	GAT
															G		A			
								CDR3												
99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114					
GAG	GCT	CGT	TAT	TTC	TGC	CAG	TCC	TAT	GAC	AAC	AGC	CTG	ACT	GGC	TGG					

results show that the use of Vλgenes in POEMS is significantly restricted. The two lambda chain sequences matched Vλ1 and could be assigned to the IGLς40-01 or 1e germline. The same study was carried out in amyloidosis and multiple myeloma. In multiple myeloma, only 28 Vλlight chain genes have been analyzed.[5-7] The germline 1e is used only once. In amyloidosis 94 Vλlight chain genes have been analyzed.[8,9] The germline 1e was used in two cases A restriction in the expression repertoire of peripheral blood lymphocytes was documented by Ignatovich and by Farner.[9] In these studies 1e was used in 13% and 5% respectively.[9]

Restricted use of λ gene and evidence of antigen driven selection (high R/S mutation ratio in the CDR of our first case and a low R/S ratio in the FR of our second case) were documented by the above method. Antigen driven selection being a clonal selection, it is likely to occur before cancer transformation, when clonal expansion is still strongly regulated.[10] When driven by such an antigen, clonal expansion does not equate to an auto antibody function of the secreted M-component. Such M-components are a minority in the literature. However, the occurrence of the same three (aminoacid replacing) substitutions in the two observations suggests that antigen binding may be relevant. The preferential use of germline 1e must be confirmed in other cases and its exact role in the pathogenesis of the syndrome should be demonstrated.

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