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Letter to the Editor

Frequency and characteristics of pruritus in patients with monoclonal gammopathy: a case-control study

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Dear Editor,

Chronic pruritus (CP) is a frequent symptom in many skin and systemic diseases(1), including haematological malignancies. It is described in 30% of Hodgkin lymphoma patients and in patients with myeloproliferative disorders, particularly in polycythaemia vera(2,3). Serum protein electrophoresis (SPEP) is recommended in laboratory screening for CP(4). However, the literature about pruritus in monoclonal gammopathies (MGs) is scarce(5-7). The aim of this study was to determine the frequency and clinical characteristics of pruritus in patients with MGs in comparison to controls with normal SPEP results.

Cases and controls were selected on SPEP performed at the University Hospital of Brest between 2014 and 2018. The inclusion criteria for cases were to have a monoclonal spike of at least 15 g/L for IgG, 10 g/L for IgA and 5 g/L for IgM (rates chosen because they are associated with higher risk of multiple myeloma (MM), Waldenström's macroglobulinemia (WM) and monoclonal gammopathy of clinical significance(8,9)). Controls had qualitative and quantitative normal SPEP results. Cases and controls were matched for the year of birth and sex. Patients with another haematological disease producing a monoclonal protein were excluded.

A questionnaire was sent out by post to patients, asking them if they suffered from pruritus. If yes, they answered to the Brest Questionnaire(10,11), the 5-D Itch Scale(12) and the ItchyQoL questionnaire(13). The study protocol was approved by a Jurisdictional Ethics Committee. The trial was registered on ClinicalTrials.gov (NCT03832140).

One hundred forty-one cases and 141 controls answered the questionnaire with a respective response rate of 48% and 50%. The characteristics of patients with an MG are presented in Table I. For controls, SPEP was prescribed in various conditions: stroke (41.8%), inflammatory rheumatism (10.6%), pre-biotherapy check-up (7.1%), dyspnoea (6.4%), bone pain (5%), anaemia (2.9%), and tumours (2.9%). CP without any skin disease was present in 32 cases (22.7%) and in 12 controls (8.5%). The difference was significant with an OR of 2.46 [1.14 - 5.32] (p=0.023). Only 20% of cases with CP had consulted a dermatologist for their pruritus. CP was present for a few years for 72% of patients with MGs, a few months for 24% and a few weeks for 4%. Most cases (48.3%) had started experiencing pruritus after the diagnosis of their gammopathy, 31% had started experiencing pruritus before the diagnosis, and 20.7% had started experiencing pruritus at the same time as the diagnosis. Pruritus was triggered by contact with water in only 4 cases

(12.9%). The most frequently reported associated symptoms were stinging (45.1%) and burning (38.8%). The mean 5-D Itch Scale score was 11.0 ± 5.9 (range 6 to 21) for cases. The intensity of pruritus was mild for 24.1% of cases, moderate for 6.9% and severe for 65.5%. The mean ItchyQol score was 38.7 ± 18.2 (range 22 to 73) for cases. Univariate and multivariate logistic regression analyses were performed to identify factors associated with the presence of pruritus in MGs (Table II). The only association found was with MM, which was less associated with CP than MG of undetermined significance (MGUS) and WM. No association was found between pruritus and monoclonal protein levels in MM (OR 0.97 [0.90-1.03], WM (OR 1.00 [0.93-1.06]) or MGUS (OR 1.01 [0.88-1.15]).

Our study demonstrated a significant association between MGs and pruritus. It is not an aquagenic pruritus, contrary to myeloproliferative disorders(2), which suggests different pathophysiological mechanisms. The impairment in the quality of life evaluated by the ItchyQol showed the same impairment as in patients with polycythaemia vera (37.3)(3) but a lower impairment than in haemodialysis patients (48.4)(14).

To conclude, our study highlighted that CP is 2.5 times more frequent in patients with MGs than in controls. Thus, SPEP is useful in the check-up to find the aetiology of unexplained CP.

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Table I. Demographic and clinical baseline characteristics of patients with monoclonal gammopathy (MG) and controls and a comparison of features in cases with or without chronic pruritus (CP).

		Cases (n=141)	Cases with CP without skin disease (n=32)	Cases without CP (n=96)*	Controls (n=141)
Sex n (%)	Men	76 (53.9)	17 (53.1)	52 (54.2)	76 (53.9)
	Women	65 (46.1)	15 (46.9)	44 (45.8)	65 (46.1)
Age (years)	Mean (SD)	71 (10.4)	73 (10.1)	71 (10.3)	71 (10.4)
	Median	72	74	72	72
	Range	44-92	44-88	50-92	45-91
Type of gammopathy n (%)	MGUS	45 (31.9)	14 (43.7)	26 (27.1)	
	IgG	13	5	6	
	IgA	9	3	5	
	IgM	23	6	15	
	Myeloma	63 (44.7)	8 (25.0)	48 (50.0)	
	IgG	50	7	38	
	IgA	12	1	9	
	IgM	1	0	1	
	Waldenström (IgM)	33 (23.4)	10 (31.3)	22 (22.9)	
	Type of light chain				
n (%)	Kappa	101 (71.6)	23 (71.9)	71 (73.9)	
	Lambda	40 (28.4)	9 (28.1)	25 (26.0)	
Kappa/lambda ratio at diagnosis	Median	2.9	1.7	3.8	
	Range	0.01-2882	0.09-573	0.01-2882	
Monoclonal protein levels (g/l)	Mean (SD)	29.6 (15.8)	24.4 (10.1)	30.3 (16.2)	
	IgG Median	24.4	22.3	24.7	
	Range	13-98	13-47.3	14-98	

IgA	Mean (SD)	18.5 (7.4)	12.6 (2.6)	21.2 (7.3)
	Median	17	11.4	21.3
	Range	7.0-31.5	10.6-17	10.2-31.5
IgM	Mean (SD)	16.5 (11.2)	15.9 (10.2)	16.8 (11.8)
	Median	14.2	15	13.9
	Range	3.4-68	3.4-39.1	4.5-68
Diagnosis of an MG	< 1 year	17 (12.2)	6 (18.8)	10 (10.4)
	1-5 years	67 (47.8)	15 (46.9)	51 (53.1)
	6-10 years	37 (26.4)	7 (21.9)	21 (21.9)
	> 10 years	19 (13.6)	4 (12.4)	14 (14.6)
	Missing value	1	0	0

MGUS: Monoclonal gammopathy of undetermined significance.

* Patients who had had pruritus and patients with CP with skin disease were excluded.

Table II. Factors associated with the presence of pruritus in monoclonal gammopathies. Univariate and multivariate logistic regression models were used to assess the association of covariates with the presence of pruritus. The covariates examined were sex, age, the type of gammopathy, the type of heavy chain, the type of light chain, heavy chain levels at diagnosis, and the kappa/lambda ratio at diagnosis. An adjustment on age and sex was then added because of a known association with pruritus.

		Odds Ratio (95% CI)	p-value
Univariate logistic regression			
Sex (male)		0.96 (0.43-2.16)	0.92
Age		1.02 (0.98-1.06)	0.41
Gammopathy	Ref MGUS		
	Myeloma	0.31 (0.11-0.82)	0.02
	Waldenström	0.84 (0.31-2.26)	0.74
Heavy chain	Ref IgA		
	IgG	0.95 (2.28-3.84)	0.94
	IgM	1.47 (0.45-5.81)	0.54
Monoclonal protein levels		0.97 (0.93-1.002)	0.10
Light chain lambda*		1.11 (0.44-2.67)	0.82
Kappa/lambda ratio		0.998 (0.994-1.000)	0.28
Multivariate logistic regression			
Sex (male)		0.96 (0.41-2.27)	0.93
Age		1.01 (0.97-1.06)	0.61
Gammopathy			
	Myeloma	0.31 (0.11-0.83)	0.02
	Waldenström	0.81 (0.28-2.30)	0.69

* ref light chain kappa.