and nature of *BCL-6* mutations found in PBL did not show striking differences to those of other extranodal lymphomas. In our series, 14 mutational events were identifiable in the 8 mutated cases, with 50% of the mutated cases harboring more than one mutation. All the mutations were single base-pair substitutions: 5 transitions (36%) and 9 transversions (64%). The most frequent substitutions corresponded to C-T transition (3/14=21%) and to C-G transversion (3/14=21%). The *BCL-6* mutations found in PCBCL are detailed in Table 1.

We also investigated the genotypic prevalence and allele frequency of two previously described polymorphisms 397 (G or C) and ΔT520. In accordance with literature data, we found the 397C and G polymorphic alleles in, respectively, 11/46 (24%) and 35/46 (76%) cases and the 520DT polymorphic allele in 18/46 (39%) cases.

In conclusion, the low frequency of mutations of the 5' non-coding region of the *BCL-6* gene found in PCBCL reinforces the observation of heterogeneity in the FCCL category as defined by the EORTC, and supports a marginal zone B-cell origin for most of these cases.

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Key words: cutaneous lymphoma, extranodal non-Hodgkin's lymphoma, primary cutaneous B-cell lymphomas, BCL-6 gene, BCL-6 mutations.

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Monoclonal Gammopathies

Effect of statins, smoking and obesity on progression of monoclonal gammopathy of undetermined significance: a case-control study

Interleukin-6 (IL-6) and C-reactive protein (CRP, a surrogate marker for IL-6) are important in monoclonal gammopathy of undetermined significance (MGUS) and myeloma. Smoking and obesity may elevate CRP levels, while statins decrease CRP levels. A case-control study in 200 MGUS patients found that statin use, smoking history and obesity do not affect MGUS progression.

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Monoclonal gammopathy of undetermined significance (MGUS) occurs in approximately 3% of persons older than 70 years.[1] The risk of MGUS progressing to multiple myeloma (MM) or a related disorder is approximately 1% per year.[2] C-reactive protein (CRP) is a surrogate indicator of interleukin-6 (IL-6) level.[3] Elevated CRP and IL-6 levels are adverse prognostic factors in MM. Smoking and obesity are positively associated with elevated CRP levels.[4,5] Conversely, hydroxymethylglutaryl-CoA reductase inhibitors (statins) are known to decrease CRP. Simvastatin induced death in MM cell lines,[6] and recent data suggest that statin use is associated with a reduced risk of some forms of cancer.[7] Studies using the Radl myeloma model also support the potential benefit from statins.[8] Durie and Mundy studied 409 myeloma patients, 34 of whom took a statin prior to developing myeloma.[8] There was a trend toward less severe bone disease (lytic lesions and/or osteoporosis) in patients receiving a statin, with only a 14% incidence of severe bone disease in patients on statins for more than five years.

So far, no study has evaluated the effect of statins, smoking, or obesity on progression of MGUS to MM or related disorders. We hypothesized that statin use may have protective effects on MGUS progression and that smoking and obesity might result in increased MGUS progression.

Following approval by our Institution Review Board, we conducted a case-control study in the 100 most recent patients with MGUS seen at Mayo Clinic Rochester who had progression to MM (or related malignancy) at least one year after the diagnosis of MGUS (Table 1). Progression was defined as the diagnosis of any of the following: MM, plasmacytoma, macroglobulinemia, osteosclerotic myeloma, primary amyloidosis (AL), IgM heavy chain with lymphoma, lymphoproliferative disorder with IgM-type protein, or chronic lymphocytic leukemia (CLL) with IgM-type protein. Additionally, 100 controls with MGUS who did not progress were matched by age, gender, and year of MGUS diagnosis. Statin use prior to the date of diagnosis of MGUS progression for each case and the

Table 2. Statin use in MGUS cases (progression) and MGUS controls (no progression).

Statin Use	*Cases*	*Controls*	*Odds Ratio*	*95%CI*	*p value*
Prior to progression/index date	15	13	1.18	0.53-2.63	0.839
>6 months prior to progression/index date	14	13	1.09	0.48-2.45	1.000
>1 yr prior to progression/index date	12	13	0.91	0.39-2.11	1.000
>4 yrs prior to progression/index date	6	6	1.00	0.31-3.21	1.000

corresponding *index* date for the matched control was determined from detailed review of medical records. Of the 100 case of MGUS that progressed, 58 progressed to MM, 4 to plasmacytoma, 17 to macroglobulinemia, 16 to AL, 3 to lymphoma, 1 to osteosclerotic MM, and 1 to a lymphoproliferative disorder with IgM-type protein. Progression occurred at a mean of 56 months (range, 12-140 months) after recognition of MGUS.

Fifteen cases and 13 matched controls had used statins prior to progression or the comparable index date, respectively (odds ratio [OR], 1.18; 95% CI, 0.5-2.6; p=0.839). There was no evidence that statins had a protective effect against MGUS progression, regardless of the duration of use (Table 2). Fifty of the control patients and 54 of those with MGUS progression had a smoking history; therefore, smoking is not a prognostic indicator of MGUS progression (OR, 1.17; 95% CI, 0.67-2.05; p = 0.671). We also evaluated the effect of obesity, defined as a body mass index (BMI) greater than 30 kg/m^2. There were 36 obese patients among the controls and 27 among the cases (OR, 0.66; 95% CI, 0.36-1.22; p = 0.240) indicating that obesity did not have a significant effect on MGUS progression. Our results were somewhat unexpected since statins have been shown to decrease CRP, and statins have recently been associated with a reduction in prostate and renal cancer.[7] Statins stimulate bone formation in cultured osteoblasts in mouse neonatal calvaria and cortical bone by increasing the synthesis of bone morphogenic protein-2.[9] However, statin use did not improve fracture risk or bone density in the Women's Health Initiative Observational Study.[10] We thought we might see an *anti-myeloma* effect independently of a direct effect of statins on bone, although the duration of statin use may not have been long enough to detecting a protective effect against MGUS progression. It is also possible that subgroups of MGUS patients with elevated CRP levels might benefit from statin use. Since appropriate serum samples were not available, the effect of statins on CRP levels in patients with MGUS or myeloma were not assessed in this study. Another limitation due to the retrospective nature of this study was that patients were taking a variety of statins at different doses and the duration of therapy was not homogeneous. The small numbers of statin users limited our ability to characterize subgroups further, based on type and dose of statin use.

In summary, although our study may have been underpowered, our report suggests that statin use, smoking history and obesity do not have an effect on MGUS progression. Further studies are needed to determine factors responsible for progression in MGUS.

Table 1. Characteristics of MGUS cases (progression) and MGUS controls (no progression).

	Controls	*Cases*
Age (years), mean (range)	67 (37-87)	67 (37-87)
Gender		
Male	62	62
Female	38	38
Ig Heavy Chain		
G	64	44
M	18	20
A	10	24
D	0	2
Biclonal	2	5
None detected	6	6
Ig Light Chain		
κ	55	56
λ	45	37
Biclonal	0	7
Smoker	50	54
BMI (kg/m^2), mean (range)	28.2 (17.9-48.0)	28.6 (18.9-49.5)
Obesity (BMI >30 kg/m^2)	36	27

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Key words: MGUS, hydroxymethylglutaryl-CoA reductase inhibitors, statin, myeloma.

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Multiple Myeloma

Xenobiotic gene polymorphisms and susceptibility to multiple myeloma

Genetic variations in the activity of xenobiotic enzymes may predict susceptibility to multiple myeloma (MM). In a case-control study, 90 Australian Caucasians with MM had significantly higher incidences of GST T1 null, PON1 BB and NAT2 slow acetylation genotypes, but no difference in polymorphism frequencies for GST M1, NAT1, and CYP1A1 when compared to 205 controls.

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All higher species have evolved complex enzyme systems for protection against environmental toxins. The human xenobiotic metabolizing system comprises two main classes of enzymes: phase 1 cytochrome P-450 (CYP) enzymes which bioactivate procarcinogens to genotoxic electrophilic intermediates, and phase 2 enzymes, including glutathione S-transferases μ and τ (GST M1 and GST T1), paraoxonase (PON1) and N-acetyltransferases 1 and 2 (NAT1 and NAT2) which conjugate the intermediates to excitable hydrophilic derivatives, completing the detoxification cycle. It is now widely believed that interindividual differences in susceptibility to malignancy may be mediated in part through variability in the xenobiotic enzyme system. In support of this contention, genetic polymorphisms that result in altered or absent activity of these enzymes have been consistently shown to be risk factors for the development of numerous malignancies, including non-Hodgkin's lymphoma (NHL).[1]

Although epidemiological studies have identified exposure to pesticides and solvents (including dioxin, dichlorodiphenyl-trichloroethane (DDT) and benzene)[2-4] as risk factors for developing MM, no one has investigated the role that differential detoxification of these carcinogens may play in the pathogenesis of the disorder. Furthermore, MM incidence rates are strongly correlated with race,[5] providing evidence for a genetic component to disease susceptibility. Therefore, the aim of this study was to determine whether inheritance of particular polymorphisms in the xenobiotic genes GST M1, GST T1, PONI, NAT1, NAT2, and/or CYP 1A1 are associated with increased risk of MM.

We conducted a case-control study using peripheral blood or bone marrow biopsy specimens from 90 Caucasian individuals (63 males and 27 females), aged 41 to 95 years (median age of 67 years), with a confirmed diagnosis of MM according to the United Kingdom Medical Research Council (MRC UK) definition. All patients were recruited from the Newcastle Mater Misericordiae Hospital, Newcastle, NSW and the Alfred Hospital, Melbourne, VIC, in Australia. The majority of samples were obtained at the time of diagnosis (n=61) or within the first (n=15) or second year (n=9) following diagnosis. The control group consisted of 205 healthy Caucasian volunteer bone marrow donors aged 18 to 65 years. The research protocol was approved by the Hunter Area Research Ethics Committee and informed consent was

Table 1. Comparison of GST T1, GST M1, PON1, NAT1, NAT2, and CYP1A1 polymorphism frequencies in cases and controls (univariate analysis).

Polymorphism		*MM patients n = 90*		*Controls n = 205*		*Odds ratio*	*95% confidence interval*	*p value*
		n[a]	*(%)*	*n*[a]	*(%)*			
GST T1	pos	68	(76)	176	(86)	1.00		
	null	22	(24)	29	(14)	1.96	1.06-3.65	0.04
GST M1	pos	45	(50)	95	(46)	1.00		
	null	45	(50)	110	(54)	0.86	0.53-1.42	0.6
PON1[b]	AA	33	(37)	103	(52)	1.00		
	AB	41	(45)	74	(37)	1.73	0.97-3.10	0.05
	BB	16	(18)	22	(11)	2.27	1.06-4.76	0.04
NAT1[c]	rapid	32	(43)	83	(42)	1.00		
	slow	43	(57)	115	(58)	0.97	0.56-1.67	0.9
NAT2[d]	rapid	31	(34)	98	(50)	1.00		
	slow	59	(66)	98	(50)	1.89	1.14-3.26	0.01
CYP1A1	-/-	69	(78)	159	(82)	1.00		
	-/+, +/+	20	(22)	34	(18)	1.36	0.71-2.50	0.3

[a]Totals vary due to incomplete genotyping data for some individuals. [b]AB vs AA and BB vs AA. [c]NatI rapid acetylators consist of genotypes: 4/10,10/10, 10/11, whilst genotypes 4/4 and 4/11 are considered slow. Odds ratio for slow vs rapid. [d]NAT2 rapid acetylators consist of all genotypes containing allele 1 (ie.,1/1, 1/2, 1/3, 1/4), whereas any other combination of the four alleles produces a slow acetylation phenotype. Odds ratio for slow vs rapid.