

Familial multiple myeloma. Two more families

Research Article

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Abstract: The authors report on two multiple myeloma sibling pairs. In the absence of a known disease-specific marker one can only speculate on an explanation: is it because of inherited errors or is it related to the same environmental exposure, or both? In this study HLA typing and metabolizing enzyme polymorphism studies have been carried out with the aim of finding inherited similarities in the siblings or characteristics that might differ from the average population. Sibling pair 1 shared an HLA haplotype. Sibling pair 2 shared only HLA-B51, DR4, DRw53, DQ3. Sibling 1/1 was *GSTT1* / *GSTM1* null and *GSTP1 Ile105Val*; sibling 1/2 was a *GSTT1* / *GSTM1* heterozygote and *GSTP1 Ile105Val*; sibling 2/1 and 2/2 were *GSTT1* heterozygotes and shared *GSTM1* null / *GSTP1 Ile105Ile*. The siblings had identical light chain or heavy chain secretion, or both. The similarities found in the inherited factors together with the same environmental exposure in the siblings' first 20 years of life imply that the development of the same disease cannot be a coincidence.

Keywords: Henoch-Schönlein purpura • Familial Multiple Myeloma • Genetic polymorphism • Susceptibility to cancer

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1. Introduction

It is always an intriguing puzzle when there is a frequent occurrence of a non-contagious disease in the same family. This is the case in familial multiple myeloma (MM) with the involvement of siblings in most instances. Multiple myeloma is responsible for one percent of all cancer deaths in the western world. Familial myeloma however is a rare entity.

In the absence of a disease-specific alteration – like that of the *bcr/abl* gene rearrangement in chronic myeloid leukemia – one can only speculate on the reasons for such a development. Did it develop as a consequence of inherited errors or result from environmental damage the siblings were exposed to in their early years living together in the same environment, or both? It is of the utmost importance therefore to publish as many

as possible of the cases found all over the world including details of their biological characteristics. In this spirit herewith the authors present two more families with multiple myeloma in siblings.

2. Material and Methods

HLA-A, -B and -C typing was performed by the standard NIH micro-lymphocytotoxicity method [1]. HLA-DR and -DQ antigens were determined by DNA based PCR-SSP technique [2]. *GSTM1* *GSTT1* genotyping was performed by multiplex PCR essentially according to earlier enzyme polymorphism studies [3]. *GSTP1 Ile105Val* genotypes were identified according to the method of Ozawa et al. except that Thermoprime Plus

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Table 1. Clinical data of the two multiple myeloma sibling pairs.

Siblings	gender	Age*	paraprotein	Blood group	Karyotype/FISH	Environmental exposure
1/1	F	68	IgG kappa	B-	N/N	Passive smoking in childhood
1 / 2	M	66	IgG kappa	A+	N/N	Passive smoking in childhood
2/1	M	54	Kappa light chain	O+	N/N	Aromatic paints
2/2	M	48	IgG kappa	B+	N/+11	Aromatic paints, benzene

Age*: age at diagnosis, N: normal

Table 2. HLA- RESULTS.

Sibling 1/1	(F)						
	A	B		Cw	DR	DRw	DQ
a	2	63	(Bw4)	7	14	52	5
b	1	57	(Bw4)	6	4	53	8
	DRB1*	DRB3*	DRB4*	DRB5*	DQB1*	DPB1*	
a	14XX	01-03			05XX		
b	04XX		01		03XX		
Sibling 1/2	(M)						
	A	B		Cw	DR	DRw	DQ
a	2	63	(Bw4)	7	14	52	5
c	33	14	(Bw6)		1		
	DRB1*	DRB3*	DRB4*	DRB5*	DQB1*	DPB1*	
	14XX	01-03			05XX		
	01XX						
Sibling 2/1	(M)						
	A	B		Cw	DR	DRw	DQ
	11	51	(Bw4)	6	4	53	3
		13	(Bw4)		7	53	2
	DRB1*	DRB3*	DRB4*	DRB5*	DQB1*	DPB1*	
	04XX		01		03XX		
	07XX		01		02XX		
Sibling 2/2	(M)						
	A	B		Cw	DR	DRw	DQ
	1	8	(Bw6)	7	4	53	3
		51	(Bw4)		15	51	6
	DRB1*	DRB3*	DRB4*	DRB5*	DQB1*	DPB1*	
	04XX		01		03XX		
	15XX			01-02	06XX		

The 1st siblings share a haplotype. The 2nd siblings share only some of the HLA antigens (HLA-B51, DR4, DRw53, DQ3); without family typing it is not possible to prove, that those were inherited from the same parent.

DNA polymerase (Abgene, Epsom, Surrey, UK) was used for catalysing the PCR reaction [4]. Results and clinical data are shown in Table 1-3. Genetic testing of siblings was carried out with their informed consent.

3. Results

The siblings had identical light chain or heavy chain secretion or both and both had been exposed to known mutagens in their first 20 years of life (Table 1). Although blood group B was present in two of the four persons it

Table 3. GST metabolizing enzyme polymorphism results.

	<i>GSTT1</i>	<i>GSTM1</i>	<i>GSTP1</i>
1 / 1	0	0	Ile/Val
1 / 2	1	1	Ile/Val
2 / 1	1	0	Ile/Ile
2 / 2	1	0	Ile/Ile

Sibling 1/1: *GSTT1* / *GSTM1* null and *GSTP1* Ile/Val; Sibling 1 / 2: *GSTT1* / *GSTM1* heterozygote and *GSTP1* Ile/Val; Sibling 2/1 and 2/2: *GSTT1* heterozygote and shared *GSTM1* null / *GSTP1* Ile/Ile. Interestingly Siblings 2/1 and 2/2 had identical polymorphisms concerning all the metabolic enzymes tested and siblings 1/1 and 1 / 2 were identical only in the homozygosity in the *GSTP1* polymorphism.

has previously been pointed out that is not the case in a large cohort of MM patients [5]. Karyotype analysis showed only a single alteration (gain of chromosome 11) in sibling 2/2.

Sibling pair 1 shared a haplotype. Sibling pair 2 shared only HLA-B51, DR4, DRw53, DQ3 (Table 2). Metabolizing enzyme polymorphism results indicated that Sibling 1/1 was *GSTT1* / *GSTM1* null and *GSTP1* Ile105Val; Sibling 1/2 was a *GSTT1* / *GSTM1* heterozygote and *GSTP1* Ile105Val; Sibling 2/1 and 2/2 were *GSTT1* heterozygotes and shared *GSTM1* null / *GSTP1* Ile105Ile (Table 3). Both siblings had wild type for H63D and C282Y polymorphism of the HFE gene (not shown).

4. Discussion

In the process of carcinogenesis environmental genotoxic exposures and inherited susceptibility may overcome defence mechanisms such as DNA repair and tumor suppressor gene activities. Recently it has been proposed that diseases developing in the elderly evolve because of failure of the ageing protective mechanisms rather than because of the accumulation of toxic compounds [6,7]. In this study we point on that this might be only one possible explanation among many, emphasizing the importance of inherited traits and environmental exposures endured in early youth.

The sad example of secondary leukemia is evidence that cytostatics that form DNA adducts can induce prolonged sister chromatid exchange (SCE) induction and so contribute to leukemic transformation, in contradistinction to those compounds that are negative in the so-called SCE test [8]. These findings would support the concept of agent-specific carcinogenesis. In the following discussion we reflect on the question from the point of view of inherited defence mechanisms provided by human metabolic enzymes.

The enzymes of the glutathione S-transferase system (GST) catalyze the conjugation of compounds of carcinogenic potential rendering them less toxic. Genes coding for the GST mu I (*GSTM1*), theta 1 (*GSTT1*) and *GSTP1* metabolizing enzymes are polymorphic in humans, and in the case of the “null phenotype” this preventative activity is absent. Concerning *GSTP1* a single nucleotide polymorphism (Ile105Val) results in a variant enzyme with lower thermal stability and altered catalytic activity. However, the literature discussing the relationship of enzyme polymorphism and disease development is controversial. In cohorts of 58 and of 86 MM patients there was no difference in the polymorphism of these detoxifying enzymes in comparison to the average population [9,10]. In contrast, according to the study of Lincz et al. there was a higher incidence (22 of 68) of *GSTT1* null genotype in cases of multiple myeloma than in controls (29 of 176) [11]. Others have found that alterations in enzyme polymorphisms lead to significant differences in drug availability, consequently in drug effectiveness and therefore in prognosis [12].

The inherited defect in the hemochromatosis gene (*HFE*) causing iron overload confers oxidative stress to tissues predisposing them to malignant transformation [13-15]. In our present study the two pairs of siblings examined were negative for C282Y and H63D mutations. This finding is in concordance with earlier results indicating that MM patients are less involved in this polymorphism than the average population [16,17].

What is it then that predisposes families to the development of this B-cell clonal disease? And why do not all family members acquire the disease? Moreover, is there any inherited characteristic known to be associated with the development of multiple myeloma at all?

HLA associations were studied to try to answer these questions.

Grobois B. reported on 15 MM families. One pair of siblings who had been HLA typed were identical in A1, A2, B15, B41 antigens. In another report, the same author introduced two brothers who were completely identical in A2, B12, BfS, DR4, B27BFS, DR2GLO1 antigens [18,19]. Engelhardt M. et al. found a high incidence of monoclonal B-cell diseases in the siblings of patients with MM who were offering themselves as allogeneic donors. The prevalence of monoclonal B-cell disease in asymptomatic siblings of myeloma families was 29,6%. HLA-A9 was present in 3 out of 5 families where all the siblings had monoclonal B-cell disease [20]. In a cohort of 125 MM patients, thirty had 39 relatives suffering from several tumors and 28 MM patients had second primary malignancies as well. A 40-fold tumor incidence increase in MM families was found in contrast to the average population [5].

There are many other studies presenting examples of familial occurrence of hematological malignancies [21-23].

Studies in unrelated MM have shown significant association of Cw2 or B18 alleles to the process [24,25]. These data reflect the fact that although there is not really a general disease-specific HLA profile for MM, in certain cases the similarities or differences in the HLA antigens might be important to better the understanding of the disease.

5. Conclusions

Similarities found in siblings concerning the *GSM1*, *GST1* or *GSTP1* metabolizing enzyme genes or HLA markers are not surprising. In the first twenty years of life, staying in the same environment will probably lead to similar

disease characteristics in siblings. In the development of MM, as in the case of other malignancies, the type of exposure, the inborn features of metabolism and repair mechanisms are equally important factors. From these family studies one might emphasize the importance of chronic carcinogen exposure endured in early years of life in the etiology of a disease manifesting in the elderly. In concordance with previous studies we might also conclude that the development of MM in siblings is not especially more frequent than that of other malignancies in the patients' family, but significantly more than that experienced in the average population. The authors therefore suggest patient and family screening for cancers, emphasizing the importance of early detection and prevention by changing lifestyle to avoid genotoxic exposure as much as possible.

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