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Mycosis Fungoides and Vitamin D Status: Analyses of Serum 25-Hydroxyvitamin D Levels and Single Nucleotide Polymorphisms in the Vitamin D Receptor Gene

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ABSTRACT Various types of cancer, including melanoma and non-melanoma skin cancer, are associated with vitamin D receptor (VDR) polymorphisms. However, few studies have addressed VDR polymorphisms in patients with mycosis fungoides (MF), and previous studies have reported conflicting results. Aim of this case-control study was to assess the correlation between VDR single nucleotide polymorphisms (SNPs) *Cdx2*, *Fok1*, *Apa1*, *Bsm1*, and *Taq1* and MF. Venous blood samples were collected from 41 patients with MF and 59 age- and sex-matched healthy controls. VDR genotypes of both groups were analyzed. Serum vitamin D levels of patients with MF were also analysed among varying stages and VDR genotypes.

Vitamin D levels were significantly low (<30 ng/mL) in 87.9% of the patients (P<0.001). No associations were found between *Apa1*, *Cdx*2, *Fok1*, and *Bsm1* SNPs and MF. However, *Taq1* polymorphisms were higher in the healthy control group (P<0.001). Our study supports the claim that vitamin D deficiency is common in patients with MF. On the other hand, our findings suggest that *Taq1* polymorphisms may be associated with decreased susceptibility to MF. Therefore, VDRs may have complex and heterogeneous effects on the pathogenesis of MF.

KEY WORDS: calcidiol, cutaneous T-cell lymphoma, mycosis fungoides

INTRODUCTION

Mycosis fungoides (MF) is the predominant subtype of primary cutaneous lymphomas (PCL) categorized as extra-nodal non-Hodgkin lymphomas. According to the World Health Organization (WHO) and European Organization of Research and Treatment of Cancer (EORTC), two large PCL groups have been identified: cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL) (1). T-cell lymphomas predominate in the skin and mostly present as MF, which is a clonal expansion of CD4 positive ($CD4^+$) cells (1-3).

Vitamin D is a fat soluble pro-hormone synthesized by keratinocytes from 7-dehydrocholesterol with the induction of ultraviolet B radiation (UVR) or obtained from nutritional sources (vitamin D rich foods and supplements). Tests for circulating vitamin D detect 25-hydroxyvitamin D (25[OH]D) or calcidiol (4). Calcitriol or 1,25-dihydroxyvitamin D3 ($1,25[OH]_2D_3$), is the bioactive metabolite of the vitamin D endocrine system (VDES) and binds the vitamin D receptor (VDR) (5). VDES has well known effects on some main biological processes including serum

calcium concentrations, skeletal homeostasis, and cell proliferation and differentiation (4,6,7). Recently, growing evidence of functions of vitamin D on cell death, invasion, and metastasis has lead scientists to directly address the association between vitamin D levels, VDR polymorphisms, and skin cancer (8-10). VDR is activated with or without $1,25[OH]_2D_3$ during hair follicle cycling and interfollicular epidermal differentiation (IFE). Vitamin D also has potential roles in clearance of UVR-induced mutations in keratinocytes (11). Factors disrupting VDES, such as VDR deletion, predisposes UVR- or chemical-induced tumor formation (12,13).

To date, there have been numerous studies on vitamin D and non-Hodgkin lymphomas (NHL); however, conflicting results leave the exact relationship unclear (14-18). Distinct VDR single nucleotide polymorphisms (SNPs) have been found in association with an increased risk of lymphoma (19). Association of poorer outcomes and 25(OH)D insufficiency has been suggested in patients with NHL, including peripheral T-cell lymphomas (20). While the role of VDES in NHL patients has been elucidated in recent years, there is a paucity of data addressing patients with CTCL. Recently, it has been reported that vitamin D levels are drastically lower (<30 ng/mL) in 76.9% of patients with CTCL (21,22). Mrotzek *et al.* reported that with sufficient serum levels of vitamin D, apoptosis can be induced in CTCL cells expressing VDR (23). Distinct VDR SNPs (*Taq1*, *Fok1*, and *Bsm1*) have been studied in patients with MF (22). Additionally, the SNPs *Apa1* and *Cdx2* are associated with lung, colorectal, prostate, and breast cancers (24-29). Gandini *et al.* presented the relevance of *Taq1*, *Fok1*, *Bsm1*, *Apa1*, and *Cdx2* SNPs in various cancer types, including skin cancer (30). There is only one report of three SNPs (*Fok1*, *Bsm1*, and *Taq1*) in patients with MF (22). However, *Cdx2* and *Apa1* have not been studied within the context of MF. Therefore, in this study, we aimed to establish whether there is an association between MF and *Cdx2* and *Apa1* SNPs in VDR.

PATIENTS AND METHODS

Participants

This case-control study was carried out in our dermatology clinic. Between January 2016 and September 2016, 41 patients (24 men, 17 women) with MF at various stages were recruited. The control group included 53 age- and sex-matched healthy volunteers. Demographic and clinical characteristics are shown in Table 1. Written informed consent was obtained from all participants. All patients were diagnosed based on clinical, histopathological, immunophenotypical, and T-cell receptor gene rearrangement criteria. Each patient was staged according to the criteria of the EORTC (31). Patients with any known additional systemic disease or patients receiving vitamin D supplementation therapy were excluded.

Treatment modalities and responses of patients were summarized in Table 2. Definition of response in the skin has been performed based on modified Severity Weighted Assessment Tool Score (mSWAT) (32).

Ethics statement

This study was conducted according to the ethics principles expressed in the Declaration of Helsinki and approved by the local ethics committee.

Samples

Serum levels of 25-hydroxyvitamin D (Roche Diagnostics, Mannheim, Germany) of 41 patients with MF and controls were analysed to investigate the association between disease characteristics (stage, lesion type, CD4/CD8, disease duration, and response to treatment) and baseline vitamin D levels. A competitive electrochemiluminescence protein assay (Roche Diagnostics, Mannheim, Germany) was performed to determine serum vitamin D levels. Values of less than 30 ng/mL and 20 ng/mL were considered vitamin D insufficient and deficient, respectively. Patients with low levels of vitamin D were treated with appropriate supplementation. Venous blood samples (5 mL) of patients and controls were drawn to determine VDR SNP polymorphisms.

Analysis of polymorphisms

Cdx2 (rs11568820), *Fok1* (rs2228570), *Bsm1* (rs1544410), *Apa1* (rs11168271), and *Taq1* (rs731236) variants were analysed with the SNaPshot® Multiplex System (Applied Biosystems, Life Technologies, USA) using primers designed in-house. Fragment analysis was performed on an ABI 3130 Genetic Analyzer (Applied Biosystems). GeneMapper® Software version 4.0 (Applied Biosystems) was used for data analysis.

Statistical analysis

All statistical calculations were performed using the IBM Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) 21 for Windows. Data are given as mean ± Standard Deviation (SD) or median and interquartile range. Categorical variables are presented as frequencies or percentage. Categorical data were compared using Chi square (χ^2) or Fischer tests. Mann–Whitney U test was performed for comparing numerical data of groups. Spearman's correlation test was used to assess correlation

Table 1. Baseline demographic and clinic characteristics of the study population

Characteristic		n (%)
Age*		54.2±13.3 years
Sex	Male	24 (58.5)
	Female	17 (41.5)
Disease duration months)*		50.5 (1-360)
Lesion type	Patch	32 (78.0)
	Plaque	8 (19.5)
	Tumor	1 (2.4)
Lymphadenopathy		7 (17.1)
TNM staging	T1N0	22 (53.7)
	T2N0	12 (29.3)
	T2N1	6 (14.6)
	T3N1	1 (2.4)
Stage	1a	22 (53.7)
	1b	13(31.7)
	2a	5 (12.2)
	2b	1 (2.4)
Total body surface area [μ]		6.2 (1-26)
CD4/CD8[¥]		1.86 (0.6-4)
Family history for MF		2 (4.9)

*Data presented as mean ± Standard Deviation, n: number, %: percentage

[μ] Mean percentage of the involvement and range are presented.

MF: mycosis fungoides; TNM: tumor node metastasis.

between categorical variables. Multiple logistic regression analyses were adjusted for analyzing the additive model effect of genotype distribution. Effects of dominant and recessive models were analysed by χ^2. Associations between disease and genotypes were assessed by calculating odds ratios and 95% confidence intervals. Determination of allele frequencies was performed according to the Hardy-Weinberg model. *P* values <0.05 were considered statistically significant.

Table 2. Treatments of the patients with MF and responses to therapy

Treatment Modality	n (%)
Topical*	11 (26.0)
Bexarotene gel	1 (2.4)
Narrowband UVB	20 (28.8)
PUVA	1 (2.4)
IFN+systemic retinoid	3 (7.3)
Methotrexate + retinoid	1 (2.4)
No treatment	1 (2.4)
Treatment Response[±]	
Stable disease	5
Partial response	20
Complete remission	14
Relapse	2

*Topical treatment included emollients and topical steroids.

±Treatment responses were evaluated according to the modified Severity Weighted Assessment Tool Score (SWAT).

RESULTS

The mean age of all patients was 54.2±13.3 years with a range of 22-84. The mean disease duration was 50.5 months.

Among all MF cases studied, the mean serum 25(OH)D level was 19.2±11.44 ng/mL. Levels of 25(OH)D were similar among male (15, 19) and female patients (19, 29). Vitamin D insufficiency was observed in 88% of subjects, whereas 63% were deficient (<20 ng/mL). The median and mean 25(OH) D levels were significantly lower compared with controls (*P*=0.039).

Primary MF lesion, BSA, disease duration, stage, CD4/CD8 rates, and response to treatments were not correlated with 25(OH)D vitamin levels and VDR polymorphisms. Vitamin D levels were not associated with relevant VDR polymorphisms.

The mutant allele frequencies of *Cdx2*, *Fok1*, *Bsm1*, *Apa1*, and *Taq1* and relevant nucleotide changes are presented in Table 3. There was no difference

Table 3. SNPs of VDR, nucleotide changes and allele frequencies of the Turkish population

SNP #	RFLP[α] name	dbSNP[ꝏ]	AA change	Gene	Wild type	Mutant	MAF[μ] (%)
1	Cdx2	rs11568820	-	VDR	G	A	42
2	FokI	rs2228570	M1T	VDR	C	T	35
3	BsmI	rs1544410	-	VDR	G	A	27
4	ApaI	rs11168271	-	VDR	G	T	50
5	TaqI	rs731236	-	VDR	C	T	26

[α] Restriction Fragment Length Polymorphism
[ꝏ] The single nucleotide polymorphism database
[μ] Mutant allele frequency

Table 4. SNPs of VDR among MF and control groups (CI; confidence interval)

VDR SNPs	**Control Group% (n=53)**	**MF Group% (n=41)**	**Odds Ratio (95% CI)**	***P***
Cdx2 G/A polymorphism				
Normal	67.9 (36)	56.1 (23)	1 (ref)	0.498
Heterozygous	22.6 (12)	31.7 (13)	0.59 (0.23-1.51)	
Homozygous	9.4(5)	12.2 (5)	0.63 (0.16-2.45)	
FokI C/T polymorphism				
Normal	49.1 (26)	56.1 (23)	1 (ref)	0.128
Heterozygous	41.5 (22)	43.9 (18)	1.28 (0.34-2.17)	
Homozygous	9.4 (5)	0.0 (0)	-	
BsmI G/A polymorphism				
Normal	39.6 (21)	43.9 (18)	1 (ref)	0.881
Heterozygous	45.3 (24)	43.9 (18)	1.14 (0.47-2.78)	
Homozygous	15.1 (8)	12.2 (5)	1.37 (0.38-4.94)	
ApaI G/T polymorphism				
Normal	43.4 (23)	34.1 (14)	1 (ref)	0.191
Heterozygous	28.3 (15)	46.3 (19)	0.48 (0.18-1.24)	
Homozygous	28.3 (15)	19.5 (8)	1.1 (0.38-3.37)	
TaqI C/T polymorphism				
Normal	17.0 (9)	51.2 (21)	1 (ref)	
Heterozygous	47.2 (25)	39.0 (16)	0.090 (0.024-0.34)	**<0.001**
Homozygous	35.8 (19)	9.8 (4)	0.32 (0.094-1.14)	0.081

in polymorphisms between groups. However, *Taq1* polymorphisms were significantly more frequent in the control group ($P<0.001$) (Table 4). Each allele was protective for MF (OR: 3.4 with 95% confidence interval). The *Taq1* polymorphism was associated with statistically significant reduction in risk in the recessive model (OR: 5.2 with 95% confidence interval) and the dominant model (OR: 5.1 with 95% confidence interval). We could not detect a significant *Taq1* polymorphism among clinical and laboratory characteristics including lesion type, duration of disease, family history, stage, CD4/CD8, 25(OH) D vitamin levels, and treatment responses.

DISCUSSION

Insufficiency of vitamin D is associated with higher rates of malignancies and autoimmune diseases, and many reports suggest a chemopreventive role of vitamin D in distinct malignancies (33-35). Furthermore, previous reports have addressed vitamin D status and VDR genotypes of patients with NHL, but the results were conflicting. Most studies found no relationship between vitamin D levels and NHL risk (36-38). A recent meta-analysis by Lu *et al.* supports these findings (18). Most of the studies regarding VDR genotypes (*Taq1* and *Fok1*) of patients with NHL have failed to demonstrate an association of these SNPs with overall risk of NHL (39,40).

Vitamin D is an important determinant in the differentiation of $CD4^+$ T-cells (41). In various cancer types, 1,25 D acts via VDR to inhibit proliferation and induce apoptosis of malignant clones (42). T-cells express functional VDR, and activated T-cells have the capacity to produce $1,25(OH)_2D_3$ from 25(OH)D (43). Mrotzek *et al.* recently addressed whether vitamin D controls malignant T-cell clones and demonstrated that with sufficient serum vitamin D levels, CTCL line cells expressing VDR are induced to undergo apoptosis (23). These reports emphasize the importance of VDR gene analyses in patients with CTCL.

However, there is limited data regarding the effects of vitamin D levels and VDR gene SNPs in patients with CTCL. Recently, Talpur *et al.* reported low levels of 25(OH)D in a large proportion of patients with CTCL and that correction of the deficiency and type of supplementation did not affect the overall response (21). Similarly, our current study supports a high prevalence of vitamin D deficiency in patients with CTCL (66%). However, we did not detect an inverse correlation of vitamin D levels and involved BSA of patients with MF. Of note is that there was no relationship between baseline vitamin D levels and other clinical characteristics. Indeed, not surprisingly, patients with low levels who took the supplementation therapy and patients with sufficient 25(OH) D levels at initial presentation showed similar therapy responses.

A previous study reported that vitamin D levels were significantly lower and the CC phenotype of the *Fok1* polymorphism more frequent in patients than controls (22). We found no evidence of association with *Bsm1*, *Fok1*, *Apa1*, and *Cdx2* genotypes. However, the *Taq1* polymorphism was detected more frequently (83%) in the healthy control group, whereas it was 26% in the MF group. These data suggest that *Taq1* genotype may be protective against CTCL in the Turkish population. The observed differences between studies may be related to different populations, because MF has a multifactorial etiopathogenesis involving complex interactions between heritable factors and environmental factors. Our finding that there was no significant correlation between VDR SNPs and disease duration, family history, clinical characteristics, and treatment responses is similar to previous reports.

Our study primarily addressed the relationship between VDR SNPs and MF. To the best of our knowledge, this report provides the first analysis of *Apa1* and *Cdx2* SNPs in patients with MF.

CONCLUSION

In this study, we detected low baseline vitamin D levels in patients with MF irrespective of clinical characteristics including family history, stage, TBSA, CD4/CD8 ratio, and treatment responses. Notably, among five SNPs, *Taq1* was more frequent (83%) in the control group, suggesting a potential preventive effect on the development of CTCL. However, it is not possible to make strong conclusions on VDR polymorphisms in patients with MF based on this study alone. Large epidemiologic studies are needed to provide better understanding of the exact role of VDES and VDR genotypes in MF pathogenesis.

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