Role of Polymorphisms in Adamantiades-Behçet's Disease

VIRGINIA G. KAKLAMANI, MAUREEN SADIM, YVONI KOUMANTAKI, PHEDON KAKLAMANIS, and BORIS PASCHE

ABSTRACT. ***Objective***. We previously showed that Adamantiades-Behçet's disease (A-BD) is associated with a lower incidence of malignancy compared with the general population. Transforming growth factor-ß (TGF-ß) has been shown to play a role in cartilage regeneration and is increased in patients with A-BD. We also found 2 functional polymorphisms of the TGF-ß pathway, *TGFBR1*6A* and *TGFB1*CC*, that are associated with risk of malignancy. We tested whether incidence of these polymorphisms would differ in patients with A-BD compared with healthy controls of similar age and geographic location.

Methods. We performed a case-control study including 139 cases and 128 controls from Greece. Cases and controls were genotyped for *TGFBR1*6A* and *TGFB1*CC*.

Results. We found that cases had lower incidence of *TGFBR1*6A* compared with controls (11.3% vs 13.3%, respectively). Also, the incidence of *TGFB1*CC* was lower in cases than controls (24.6% vs 27.0%, respectively). These differences were not statistically significant.

Conclusion. Although there is a suggestion that the lower incidence of *TGFBR1*6A* in A-BD patients may play a protective role against development of malignancy, larger studies would be needed to fully evaluate the role of TGF-ß and its polymorphisms in A-BD. (First Release Oct 15 2008; J Rheumatol 2008;35:2376–8; doi:10.3899/jrheum.080676)

Key Indexing Terms:
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Adamantiades-Behçet's disease (A-BD) is a chronic, relapsing multisystem disorder[1]. The pathogenesis of the disease has not been elucidated, although genetic factors, environmental agents, and immune aberrations have been implicated[2]. Treatment of A-BD includes immunosuppressive agents, such as corticosteroids and anti-transforming growth factor-ß (anti-TGF-ß) monoclonal antibodies[1,3]. Such therapies have been associated with increased risk for malignancy[4]. However, we recently showed that the risk for malignancy in A-BD patients is lower than that of the general population[5]. Other studies in patients with A-BD have had mixed findings, with both an increased and a decreased incidence of malignancy observed[5].

TGF-ß is a potent naturally occurring inhibitor of cell growth[6]. TGF-ß binds first to a type II (TGFBR2) then to a type I receptor (TGFBR1). There is growing evidence that common functional variants of the TGF-ß pathway modify cancer risk[7]. Two functional polymorphisms of the TGF-ß pathway have been described: *TGFBR1*6A*, a variant of the type I receptor of TGF-ß, has been implicated in breast, ovarian, and colon cancer and is associated with decreased TGF-ß signaling; and *TGFB1*CC*, which increases TGF-ß signaling[8] and has been shown to decrease the risk of breast cancer[7,9,10].

The role of TGF-ß in A-BD is not clear. TGF-ß has been shown both *in vitro* and *in vivo* to be protective against cartilage destruction by inducing proteoglycan synthesis and stimulating extracellular matrix synthesis[11]. There has been some suggestion that TGF-ß levels in synovial fluid in patients with A-BD are increased, although to levels not as high as in rheumatoid arthritis[12].

From the Cancer Genetics Program, Division of Hematology/Oncology, Department of Medicine, and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; Department of Hygiene and Epidemiology, Medical School, Athens University; and Department of Rheumatology, Athens Medical Center, Athens, Greece.

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V.G. Kaklamani, MD, DSc; M. Sadim, Cancer Genetics Program, Division of Hematology/Oncology, Department of Medicine, and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University; Y. Koumantaki, MD, Department of Hygiene and Epidemiology, Medical School, Athens University; P. Kaklamanis MD, Department of Rheumatology, Athens Medical Center; B. Pasche, MD, PhD, FACP, Cancer Genetics Program, Division of Hematology/Oncology, Department of Medicine, and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine.

Address reprint requests to Dr. B. Pasche, Division of Hematology-Oncology, University of Alabama, Birmingham, 1802 Sixth Ave. South, NP 2566, Birmingham, AL 35294-3300. E-mail: Boris.Pasche@ccc.uab.edu

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We hypothesized that patients with A-BD would have higher TGF-ß signaling, which would account for the decreased incidence of malignancy in this population, as well as the higher levels of TGF-ß in the synovial fluid of these patients. Therefore A-BD patients would have a lower carriership of the *TGFBR1*6A* allele and a higher carriership of the *TGFB1*CC* genotype.

MATERIALS AND METHODS

A total of 139 cases and 128 controls were genotyped as part of this study. Cases were individuals who fulfilled A-BD according to the international study group criteria[13]. Subjects from an outpatient clinic were consecutively entered in the study from 1990 to 2006. Controls were of similar ethnicity, gender, age, and race. DNA was extracted from peripheral blood lymphocytes using a commercial kit (Qiagen, Valencia, CA, USA). Genotyping was performed for *TGFBR1*6A* and *TGFB1*CC* as described for both functional polymorphisms[9]. Genotyping results were compared using the chi-square test (SPSS 13.0 software).

RESULTS

The median age of the cases was 40.9 years (range 15–68) and was not significantly different from the controls (38.0; range 15–69; Table 1). The allelic frequency of *TGFBR1*6A* among cases was lower compared to controls (11.3% vs 13.3%, respectively), although the difference did not reach statistical significance. We had expected to find fewer *TGFBR1*6A* carriers among cases, given our initial hypothesis of a lower incidence of malignancy in that population. *TGFB1*CC* was found among 24.6% of cases versus 27.0% in controls, a difference that was not statistically significant. Since the *TGFB1*CC* genotype is associated with higher levels of TGF-ß, we expected to find a higher frequency of this genotype in our cases compared with the controls[8].

DISCUSSION

Adamantiades-Behçet's disease is a chronic, relapsing multisystem inflammatory disorder. Immune abnormalities, particularly increased production of some antibodies, have been reported in patients with A-BD[1]. Treatment options include corticosteroids, cyclosporin A, methotrexate, and most recently anti-tumor necrosis factor-α monoclonal antibodies[1]. All these treatments are potent immunosuppressants and are administered to patients with A-BD for years at a time, causing concerns for development of malignant neoplasms. We were therefore surprised to find that the incidence of malignancy in our BD population was lower than expected[5]. We speculated that A-BD patients may have a favorable genetic background that protects them from developing malignant neoplasms.

There is strong evidence that the TGF-ß pathway may be implicated in cancer development[9]. *TGFBR1*6A*, a polymorphism resulting in decreased TGF-ß signaling, has been shown to increase the risk for breast, ovarian, prostate, and colon cancer[9]. We have preliminary data that also point to increased risk of lymphoma (unpublished data). Patients with A-BD seem to develop both solid and hematologic malignancies[5,14]. The incidence of hematologic malignancies has been attributed to use of immunosuppressive drugs[5,14]. Since there is evidence that *TGFBR1*6A* is associated with the development of both solid and hematologic malignancies, we chose to study this polymorphism in a A-BD patient population.

In our patient population the allelic frequency of *TGFBR1*6A* was lower, although not significantly, than that of the general population. Further, the *TGFBR1*6A* allelic frequency in our A-BD population was lower compared to most populations studied. This may provide a protective mechanism against the development of malignancy in patients with BD and may explain the increased levels of TGF-ß in the synovial fluid of patients with A-BD.

Our study has several limitations. It was conducted in a Greek population. We have previously shown in a Greek A-BD population that the incidence of malignancy is lower than expected[13]. Our data from several studies conducted in the US show that the role of *TGFBR1*6A* in cancer does not differ in different ethnic groups[5,7]. This to our knowledge is the first study of *TGFBR1*6A* in Greeks. Given that both cases and controls are of the same ethnicity, we have no reason to believe that our results would be skewed by this. Also the total number of cases and controls may not be enough to identify an association between a low-penetrance gene polymorphism such as *TGFBR1*6A* and A-BD. However, as A-BD is a rare disease, larger numbers of cases and controls will be hard to find.

This is the first study to our knowledge evaluating the relation between A-BD-related malignancy and *TGFBR1*6A*. Given the low penetrance of this polymorphism, these findings would have to be validated in a larger study.

Table 1. Patient characteristics and genotyping results in cases and controls.

		Cases, n = 139	Controls, n = 127
Age, mean (range) yrs		40.9 (15–68)	38.0 (15–69)
Male, %		64.2	44.5
Female, %		35.8	55.5
TGFBR1*6A, % (n)	9A/9A	88.7 (118)	86.7 (111)
	9A/6A	11.3 (15)	13.3 (17)
	6A/6A	0	0
TGFB1, % (n)	TT	27.6 (37)	22.7 (29)
	CC	24.6 (33)	28.9 (37)
	TC	47.8 (64)	47.8 (61)

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