Role of Polymorphisms in Adamantiades-Behçet’s Disease

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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 TGFB1*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)

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

TGF-ß is a potent naturally occurring inhibitor of cell growth. 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. 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 and has been shown to decrease the risk of breast cancer.

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. 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.

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We hypothesized that patients with A-BD would have higher TGF-β signaling, which would account for the decreased incidence of malignancy in this population, as well as the higher levels of TGF-β in the synovial fluid of these patients. Therefore A-BD patients would have a lower carrier-ship of the TGFB1*6A allele and a higher carrier-ship 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. 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 TGFB1*6A and TGFB1*CC as described for both functional polymorphisms. 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 TGFB1*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 TGFB1*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-β, we expected to find a higher frequency of this genotype in our cases compared with the controls.

DISCUSSION
Adamantiaides-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. Treatment options include corticosteroids, cyclosporin A, methotrexate, and most recently anti-tumor necrosis factor-α monoclonal antibodies. 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. 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-β pathway may be implicated in cancer development. TGFB1*6A, a polymorphism resulting in decreased TGF-β signaling, has been shown to increase the risk for breast, ovarian, prostate, and colon cancer. 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. The incidence of hematologic malignancies has been attributed to use of immunosuppressive drugs. Since there is evidence that TGFB1*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 TGFB1*6A was lower, although not significantly, than that of the general population. Further, the TGFB1*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-β 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. Our data from several studies conducted in the US show that the role of TGFB1*6A in cancer does not differ in different ethnic groups. This to our knowledge is the first study of TGFB1*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 TGFB1*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 TGFB1*6A. Given the low penetrance of this polymorphism, these findings would have to be validated in a larger study.

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