Relationship between the serum TGF β1 level and anti organ-specific antibodies in vitiligo patients

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Background: To our knowledge, there is a hypothesis regarding the association of vitiligo with other autoimmune disorders. Organ-specific autoantibodies are found more frequently in the serum of vitiligo patients. Recent studies have demonstrated the role of alterations in serum transforming growth factor-beta (TGF-beta) released from regulatory T cells in the pathogenesis of depigmentation observed in vitiligo. It has been shown that in comparison with patients without autoimmune diseases, serum TGF-beta levels increase in patients whose vitiligo is associated with autoimmune diseases. We hypothesized a relationship between serum TGF-beta levels and organ-specific autoantibodies that could predict other autoimmune diseases in vitiligo patients.

Method: Forty-five patients with a mean age of 35.96±13.34 years who had stable vitiligo since 1 year ago and involvement of up to 30% body surface area were enrolled. Organ-specific autoantibodies (ANA, anti mitochondrial Ab, anti TPO (anti thyroid microsomal Ab), anti parietal cell Ab, anti thyroglobulin Ab) and serum TGF-beta level were evaluated.

Result: Twenty-three patients (51.11%) had at least one positive organ-specific autoantibody. Anti TPO in 16 patients, anti thyroglobulin Ab in 9 patients, anti parietal cell Ab and ANA each in 5 patients, and anti mitochondrial Ab in 4 patients were positive. Mean serum TGF-beta level was 105.82±30.33; there was no significant difference in serum TGF-b level between patients with and without positive organ-specific autoantibody (P=0.26).

Conclusion: Although another study showed the relationship between serum TGF-beta levels and autoimmune disorders in vitiligo patients, we did not find a significant difference in serum TGF-beta levels in these patients regarding the positivity of organ-specific antibodies. It may be due to the fact that our patients had autoantibodies without clinical autoimmune disease except vitiligo.

Keywords: organ specific autoantibodies, transforming growth factor-beta, vitiligo

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INTRODUCTION

Vitiligo is an idiopathic acquired pigmentary disorder with circumscribed depigmented macules and patches, which are often symmetrically distributed. The disease has a global prevalence of 0.5-2% with no predilection for age, sex, or race. The mean age of onset is approximately 20

years. Vitiligo can be psychologically and socially distressing, and can lead to the impairment of the quality of life, particularly if the visible areas of the body (face, hands) are involved [1,2].

There is an autoimmune theory for the pathogenesis of vitiligo that is supported by first, the association of vitiligo with a number of autoimmune diseases (thyroid disease, diabetes mellitus, Addison's disease, and pernicious anemia); and second, the finding of organ-specific autoantibodies and circulating anti melanocyte autoantibodies in the serum of the vitiligo patients [3]. In addition, there is evidence of enrollment of cellular immunity by the immunohistologic study of the perilesional skin and T-cell analysis of the peripheral blood [3].

Recent studies have mentioned the role of alterations in serum transforming growth factor-beta (TGF-beta) released from regulatory T cells in the pathogenesis of depigmentation observed in vitiligo. In addition to the role of TGF-beta in the pathogenesis of vitiligo, Basak et al showed that serum TGF-beta levels increased in patients whose vitiligo was associated with autoimmune diseases in comparison with patients without autoimmune diseases [4,5]. The aim of this study was to assess the relationship between the serum level of TGF-beta and organ-specific autoantibodies in vitiligo patients.

PATIENTS AND METHODS

This observational – cross sectional study was performed in the dermatology clinics of Shahid Beheshti University Hospitals between March and September 2010. All patients gave signed informed consent before enrollment in this study after they received information about the study protocol.

Forty-five patients, including 26 (57.78%) women and 19 (42.22%) men, were enrolled in our study. The patients aged between 11 and 62 years of age, with a mean age of 35.96±13.34 years. A designed form including questions about duration of disease, age of onset, family history, history of any systemic or autoimmune disease, koebner phenomenon positivity, type of vitiligo (localized, generalized, segmental, acral/acrofacial) and involvement of body surface area in quartile percentiles was completed for each participant.

Inclusion criteria were as follows:

- All untreated vitiligo patients who were visited at our clinic and known cases that did not receive any systemic or topical treatment in the last year.
- Disease stability in the last year (no development of new patches, no progress of the present patches, negative koebner phenomenon).
- Involvement of the skin less than 30% of the body surface area.

All patients were referred to one laboratory and 10 cc peripheral venous blood samples were drawn from them. Blood samples were centrifuged for the collection of serum.

Half of the serum was used for analyzing organ-specific autoantibodies. Another half was frozen at -80C for later analyses of TGF-β1.

ANA, anti mitochondrial Ab, and anti parietal cell Ab were detected by indirect immunofluorescence. Anti TPO (Anti thyroid microsomal Ab) and anti thyroglobulin Ab levels were detected by electrochemiluminescence (ECL). TGF-β1 levels were detected quantitatively by the enzyme-linked immunosorbent assay (ELISA) method. ELISA tests were studied according to the manufacturer's instructions.

Statistical analysis was performed using the statistical software SPSS 16.0.0. (SPSS Inc. Chicago, IL, USA). Results are expressed as mean±standard deviation. A binary logistic regression was applied to investigate the influence of the serum TGF-beta level, age and sex of the patients on having at least one positive organ-specific autoantibody test. The odds ratio (*OR*) was calculated and presented with a 95% confidence interval (*CI*). P values less than 0.05 were considered significant.

RESULT

Forty-five patients, 19 males (42.22%) and 26 females (57.78%) with a mean age of 35.96±13.34 (range 11-62) years, who had involvement of up to 30% body surface area and stable vitiligo and did not receive any treatment since one year ago were included in the study. Organ-specific autoantibodies (ANA, anti mitochondrial Ab, anti TPO (anti thyroid microsomal Ab), anti parietal cell Ab, and anti thyroglobulin Ab) and TGF-beta levels of the patients serum were evaluated.

Anti TPO in 16 patients (35.56%), anti

thyroglobulin Ab in 9 patients (20%), anti parietal cell Ab and ANA each in 5 patients (11.11%) and anti mitochondrial Ab in 4 patients (8.89%) were positive. On the whole, twenty three patients (51.11%) had at least one positive organ-specific autoantibody.

The mean serum TGF-beta level of the patients was 105.82 ng/ml ± 30.33. The mean serum TGF-beta level of the patients with and without positive autoantibody was 100.76 ng/ml ± 30.90 (range 48.93-165.14) and 111.11 ng/ml ± 29.48 (range 40.59-160.09) respectively which showed no statistically significant difference (P=0.26) (Figure 1).

Eighteen (69.23%) out of 26 female patients and 5 (26.32%) out of 19 male patients had at least one positive organ-specific autoantibody. According to our findings, no significant difference was detected in the mean serum TGF-beta level of female and male cases (101.67±30.32 (range 40.59-165.14) in females vs. 111.50±30.21 (range 54.53-160.09) in males, P=0.29). Logistic regression analysis was conducted to evaluate the effect of the serum TGF-beta level, age and sex of the patients on having at least one positive organ-specific autoantibody. The results of the logistic regression analysis showed that only the sex variable was a significant predictor (p=0.008, OR=6.65, 95% CI= [1.634, 27.104]). The odds of having at least one positive organ-specific autoantibody were 6.65 times higher for females. The serum TGF-beta level and age of the patients did not make significant contributions to the logistic model (p=0.431 and p=0.097, respectively).

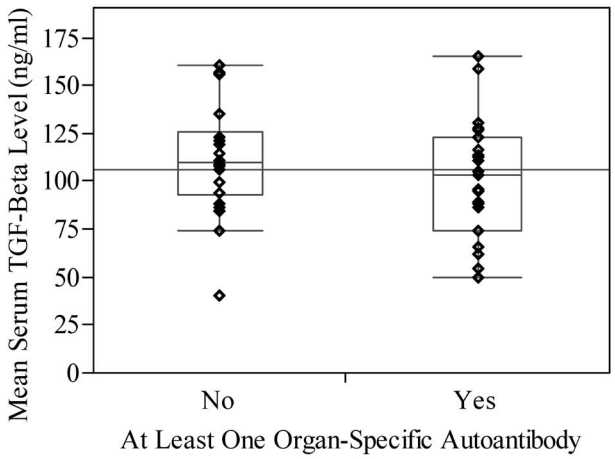

Figure 1. Levels of serum TGF-Beta in patients with vitiligo

DISCUSSION

To our knowledge, there has been a hypothesis about the association of vitiligo with other autoimmune disorders [3]. Organ-specific autoantibodies are found more frequently in the serum of vitiligo patients [3]. The existence of at least one positive organ-specific autoantibody in more than half (51.11%) of our patients was also a high percentage. In a study by Mandry et al, a significant increase was found in organ specific antibodies in vitiligo patients and their first and second degree relatives when compared to normal controls [6]. Another study showed a statistically significant increase in the frequency of organ specific antibodies such as gastric parietal cell ($p < 0.001$), thyroid microsomal ($p < 0.05$) and adrenal autoantibodies ($p < 0.05$) in vitiligo patients, without clinical signs of overt autoimmune diseases [2].

Among the organ specific autoantibodies in our study, antiTPO had the highest prevalence of positivity followed by anti TG. This finding certifies higher occurrence of thyroid autoantibodies in vitiligo patients as compared to other organ specific autoantibodies. In a study by Iacovelli et al, seven out of 13 vitiligo patients with elevated autoantibodies had anti TPO antibody [5]. As reported earlier, vitiligo has an association with autoimmune thyroid diseases and thyroid functional disorders, and the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than normal subjects [4]. So, the routine screening for thyroid disease is commonly accepted in adult patients with vitiligo due to the frequency of association with autoimmune thyroiditis [4].

None of our patients had a history or sign of autoimmune disease and the thyroid function test was normal in those with a positive titer of anti TPO and/or anti TG. It seems that having organ specific autoantibodies is not necessarily related to having autoimmune disorder although it may potentially increase the risk of these diseases.

The role of alterations in serum transforming growth factor-beta (TGF-beta) released from regulatory T cells in the pathogenesis of depigmentation in vitiligo has been mentioned in some studies [1,7]. Basak et al reported that in patients whose vitiligo was associated with autoimmune diseases, serum TGF-beta levels increased as compared with patients without autoimmune

diseases [1]. However, this level decreased in our study although not significantly.

In our study, the rate of autoantibodies positivity was higher in female than in male patients, which may be due to the reason that autoimmune diseases are more prevalent in women as compared with men; this may support the higher prevalence of autoimmune disorders in women. Moretti et al found that TGF-beta was at minimal levels in tissues of both vitiligo patients and control subjects [7]. Basak et al reported that TGF-beta levels were significantly decreased in all clinical types of vitiligo compared with control group and showed higher serum TGF-beta levels in patients with vitiligo and associated autoimmune diseases when compared to the patients without autoimmune diseases [1,8].

In the current study, we found no significant difference in the serum TGF-beta level in these patients regarding the positivity of organ-specific antibodies. The reason might be that none of our patients had clinical autoimmune disease. In conclusion, we found that the level of TGF beta, as other cytokines, may have some changes in vitiligo with other autoimmune disease; however, these changes are not very significant to confirm the hypothesis that the probability of autoimmune disorders other than vitiligo is higher in these patients.

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