Evaluation of immunological profile and clinical characteristics in patients with vitiligo

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Objective: Assess the presence of immune disorders in patients with vitiligo and the effects of low dose azathioprine and steroid as treatment.

Methods: We enrolled 190 Taiwanese vitiligo patients at a rheumatology out-patient clinic, all of whom had previously failed to respond to topical corticosteroids and photochemotherapy. We recorded clinical features, disease course, and serological data commonly used in the diagnosis of autoimmune diseases. The response to low dose of azathioprine 25 mg qd and prednisolone 5 mg qd were assessed in each of four dimensions, including skin lesion progression, new skin lesions development, less distinct vitiligo margin and pigment regeneration by physician and patient visual analog scale.

Results: 145 patients (76.32%) had simple vitiligo (no serological abnormality) and 45 patients (23.68%) had at least one serological abnormality. Of these 45 patients, 22 patients (11.58%) had systemic rheumatic disease (5 patients with systemic lupus erythematosus, 4 patients in each of psoriasis, spondyloarthropathy, and cryoglobulinemia, 2 patients with rheumatoid arthritis, and 1 patients in each of dermatomyositis, Behcet’s disease, and hypersensitive angiitis), 9 patients (4.74%) had thyroid disease, and 14 patients (7.37%) had serology abnormalities without diagnosis of specific disease. Most patients (174 patients, 91.58%) showed no more vitiligo progression and no development of new skin lesions within 2.3 ± 1.1 months. Furthermore, 64 patients (33.68%) experienced a regression of skin lesions in 5.4 ± 1.6 months, 52 patients (27.37%) experiencing a less distinct margin and 33 patients (17.37%) experiencing pigment regeneration. None of the patients reacted adversely to the treatment.

Conclusion: Our study showed a possible immune dysregulation in patients with vitiligo as evidenced by presence of abnormal immune profiles and association with other autoimmune diseases. Our data also disclosed that low dose systemic azathioprine and steroid were effective in treating this disorder.

Key words: Vitiligo, autoimmune diseases, prednisolone, azathioprine

Introduction

Vitiligo is a chronic skin disease characterized by the presence of depigmented macules that result from a reduction in the number and function of melanocytes. The precise cause is unknown, but the disease can have a negative effects on psychological well-being [1,2]. Vitiligo may result from the destruction of melanocytes by necrosis or more probably by apoptosis [3]. Genetic factors appear to play a role [4,5]. The prevalence of this disease varies from 0.1% to 2% in various populations and there is no predilection for sex or race [6-8]. The age of onset is variable, but it is generally
in the second and third decades of life [5]. The pattern of skin distribution can be generalized (most common), acral, acrofacial, localized, or segmental. A generalized distribution is characterized by symmetrically-distributed areas of depigmentation [9,10]. The disease is typically slowly progressive.

Many studies suggest that vitiligo can be considered an autoimmune disease and it has frequently been described in association with other autoimmune diseases including thyroid disorders, diabetes mellitus, alopecia areata, pernicious anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune polyglandular syndrome, and psoriasis [11-14]. The immunologic aberrations associated with vitiligo are primary or secondary events in the destruction of melanocytes. In this study, we examined the importance of identifying autoimmune diseases and immune disorders in patients with vitiligo and examined the efficacy of low dose azathioprine and steroid as treatment for vitiligo.

Material and Methods

This is an open-label study that enrolled 190 patients with vitiligo at the rheumatology clinic of DaLin Tzu Chi Buddhist Hospital (Chia-Yi, Taiwan) between January 2000 and December 2007. All patients previously failed to respond to topical corticosteroids and photochemotherapy. Patients with postinflammatory hypopigmentation, morphea, and chemical leukoderma were excluded. Thorough histories and systemic examinations were recorded. Laboratory tests included completed blood count, urinalysis, ANA, extractable nuclear antigen (ENA), C3, C4, circulating immune complex (CIC), IgG/A/M, rheumatoid factor (RF), cryoglobulin, and thyroid hormone of T3, free T4, TSH, ATA, AMiA. All patients were treated with low dose azathioprine 25 mg/day and prednisolone 5 mg once daily. The response to treatment were evaluated monthly in each of four dimensions (skin lesion progression, new skin lesions development, less distinct vitiligo margin and pigment regeneration) by physician and patient visual analog scale (VAS) and compared to the pre-treatment status.

Results

In the present study of 190 patients with vitiligo, 127 were females and 63 were males. Patient age ranged from 10 to 82 years. Peak age of onset was between 15 and 25 years. The duration of the disease before treatment ranged from 2 months to 34 years, with mean duration of 4.2 years. Duration of vitiligo was <5 years for 115 patients (60.53%) and >5 years for 75 (39.48%) patients. Twenty nine (15.27 %) patients had family history of vitiligo.

One hundred-and-forty-five patients (76.32%) had simple vitiligo (no serological abnormality) and 45 patients (23.68%) had at least one serological abnormality. Of these 45 patients, 22 patients (11.58%) had systemic rheumatic disease (5 patients with SLE, 4 patients in each of psoriasis, spondyloarthropathy, and cryoglobulinemia, 2 patients with RA, and 1 patients in each of dermatomyositis, Behcet’s disease, and hypersensitive angitis), 9 patients (4.74%) had thyroid disease, and 14 patients (7.37%) had serology abnormalities without diagnosis of specific disease (Table 1).

Table 2 lists the serological details of these 45 vitiligo patients. The major laboratory abnormalities were presence of hypocomplement (n = 22, 11.58%), abnormal thyroid function (n = 11, 5.8%), presence of ANA (n = 9, 4.74%), persistent leukopenia or lymphocytopenia (n = 9, 4.74%), hyperglobulinemia (n = 8, 4.21%), presence of rheumatoid factor. (n = 6, 3.16%), presence of ENA and presence of antis-DNA (n = 5, 2.64% each), cryoglobulin and CIC (n = 4, 2.11% each) and proteinuria (n = 2, 1.06%). Further analysis of the 45 patients with serological abnormalities indicate that 32 patients (16.8%) had one serological abnormality,
Table 2. Laboratory data in vitiligo patients

<table>
<thead>
<tr>
<th>Serology abnormality</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocomplement</td>
<td>22 (11.58)</td>
</tr>
<tr>
<td>Abnormal thyroid function</td>
<td>11 (5.80)</td>
</tr>
<tr>
<td>Antinuclear factor (ANA)</td>
<td>9 (4.74)</td>
</tr>
<tr>
<td>Leukopenia or lymphocytopenia</td>
<td>9 (4.74)</td>
</tr>
<tr>
<td>Hyperglobulinemia (IgG/A/M)</td>
<td>8 (4.21)</td>
</tr>
<tr>
<td>Rheumatoid factor (RF)</td>
<td>6 (3.16)</td>
</tr>
<tr>
<td>Extractable nuclear antigen (ENA)</td>
<td>5 (2.64)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>5 (2.64)</td>
</tr>
<tr>
<td>Circulating immune complex (CIC)</td>
<td>4 (2.11)</td>
</tr>
<tr>
<td>Cryoglobulin</td>
<td>4 (2.11)</td>
</tr>
<tr>
<td>Urine protein</td>
<td>2 (1.06)</td>
</tr>
</tbody>
</table>

*Case numbers and percentage in 190 patients with distinct serology abnormality defined as C3/C4 (90/10 mg/dL); thyroid function (TSH 0.35-5.5 IU/mL, free T4 0.7-1.8 ng/dL, T3 80-190 ng/dL); ANA (cut level: 1:40); leukopenia (4000/U/L); lymphocytopenia (1500/U/L); hypergammaglobulinemia (IgG 1600 mg/dL, IgA 400 mg/dL, IgM 250 mg/dL); RF (RF-IgG >14 IU/mL, RF-IgA > 6 unit); presence of ENA (SSA, SSB, Sm, RNP by ELISA method); anti-dsDNA (>15 IU/mL); CIC (>45 ug/mL); urine protein (≥2+, by dipstick; 3).

Patients (3.16%) had 2 serological abnormalities, 5 patients (2.63%) had 3 serological abnormalities, and 2 patients (1.05%) had more than serological abnormalities (Fig. 1).

We assessed monthly the response to treatment with low-dose azathioprine (25mg/day) and prednisolone (5mg/day) by using the physician and patient VAS. Most patients (174 patients, 91.58%) showed no more vitiligo progression and no development of new skin lesions in 2.3 ± 1.1 months. Furthermore, 64 patients (33.68%) experienced a regression of skin lesions in 5.4 ± 1.6 months, 52 patients (27.37%) experiencing a less distinct margin and 33 patients (17.37%) experiencing pigment regeneration. None of the patients reacted adversely to the treatment.

### Discussion

Vitiligo does not cause physical impairment and is often neglected by physicians. Thus, vitiligo patients do not often visit doctors and are often untreated. However, vitiligo patients can experience psychological distress or even stigmatization. Nearly 50% of vitiligo patients are not adequately informed about their disease and its treatment during initial doctor visits. Although the precise etiology of vitiligo is not known, recent studies indicate that complex genetic, immunological, and neurological mechanisms are involved in its pathogenesis [15]. Several previous studies have examined the pathogenetic aspects of this association [16,17]. In addition, vitiligo patients have a statistically significant elevation of activated T cells compared with control subjects [18]. Recently, several studies have reported vitiligo patients experience oxidative stress and the accumulation of free radicals in the epidermal layers of the affected skin [19,20] and blood [21,22].

A previous study of 2624 vitiligo probands from North America and the U.K indicated a significantly greater occurrence of certain autoimmune disorders in vitiligo probands and their first degree relatives [23]. These disorders included autoimmune thyroid disease (particularly hypothyroidism), pernicious anemia, Addison’s disease, SLE, and probably inflammatory bowel disease. In the present study, we also noted a high incidence of associated immune diseases (16.32%) (Table 1). The most common autoimmune disorder in our patients was thyroid disease (4.74%), followed by SLE (2.64%), psoriasis, spondylarthropathy, and cryoglobulinemia (2.1% each), RA (1.06%), and dermatomyositis, Behcet’s disease, and hypersensitive angitis (0.53% each). Our finding of high positive family history of vitiligo (15.27%) supports the previous finding that vitiligo is a genetically determined immune disease [24].

During the past 6 years, several new advances in the treatment of vitiligo have been reported, including narrow band UV-B phototherapy, targeted light therapy, topical immunomodulators, and calcipotriol in combination with UV radiation [25-27]. Cyclophosphamide and cyclosporine-A have also been used with variable
success. Radmanesh et al. [28] reported that azathioprine may potentiate the repigmentation effects of PUVA therapy. In present study, most of our patients responded to low dose systemic immunotherapy with prednisolone and azathioprine after 2.3 ± 1.1 months and none of our patients experienced adverse effects.

In summary, vitiligo is a systemic process that has important implications beyond the skin. We describe here the association of vitiligo with numerous immunological disorders and emphasize the importance of determining the presence of well-known autoimmune diseases. Our results also show that low dose azathioprine and steroid can successfully treat vitiligo.

References

皮膚白斑病之臨床免疫和治療的反應評估

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目的：評估白斑病人免疫調控異常以及低劑量azathioprine合併使用類固醇之臨床療效。方法：在這一個open-label的研究當中，針對190白斑病病人在一般的外用塗抹皮質類固醇和光化療的反應皆失敗後收案作治療前後評估。所有本研究的病人皆有詳盡的記錄，包括：臨床特徵、疾病進程、以及血清資料(全血球計數、尿液分析、免疫功能分析(ANA、ENA、RF、C3、C4、IgA、IgG、IgM、CIC、cryoglobulin)、甲狀腺功能(anti-thyroid antibody、T3、free T4、TSH、antithyroglobulin、antimicrosomal antibody)。病人每天接受低劑量的25 mg azathioprine(硫唑嘌呤)合併5 mg prednisolone。治療後每月皆有仔細記錄，包括白斑進展(skin lesion progression)，新白斑病變(new skin lesions development)，白斑週邊淡化(less distinct vitiligo margin)，以及新色素形成(pigment regeneration)。結果：在此研究當中，145位病人(76.32%)患有單純皮膚白斑病，並沒有血清實驗數據異常。相反地，45位病人(23.68%)合併有免疫疾病異常; 其中的9位病人有甲狀腺疾病，有22位病人符合系統性的風濕免疫疾病診斷的要素，包括5位系統性紅斑性狼瘡，4位乾癬，4位脊椎關節病變，4位冷凝球蛋白血症，2位類風濕性關節炎，1位皮肌炎，1位Behcet's disease，1位過敏性血管炎。另有14位病人有血清檢查上的數據異常但尚未有足夠條件診斷出特定的疾病。進一步分析，主要的抽血實驗檢查異常包括：補體低下、甲狀腺功能異常、ANA自體免疫抗體、持續的白血球過低、淋巴球過低、免疫球蛋白增多症和其他的異常(包括RF類風溼因子、ENA、anti-dsDNA抗體、cryoglobulin冷凝蛋白、CIC免疫複合體、蛋白尿)。分析治療反應得知大部分病人(共174位，91.58%)於低劑量的25 mg azathioprine/天和5 mg prednisolone/天治療後其皮膚的病灶不再惡化進行，也不再產生新的病灶，平均治療反應時間約2.3 ± 1.1個月；64位病人(33.68%)皮膚白斑有持續縮小，平均持續治療時間約5.4 ± 1.6個月；52位病患(27.37%)皮膚病灶的邊緣變得不明顯；33位病人(17.37%)皮膚病灶有色素再生現象。沒有病人對於此項治療產生副作用。結論：我們的研究顯示皮膚白斑病是一種免疫調控異常疾病，而且常合併其他自體免疫疾病。我們的研究結果也顯示低劑量的azathioprine和prednisolone治療此疾病有顯著療效。

關鍵詞：白斑病，自體免疫疾病，類固醇(prednisolone)，硫唑嘌呤(azathioprine)