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Report

Vitiligo vulgaris and autoimmune diseases in Japan

A report from vitiligo clinic in Kyoto University Hospital

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We reviewed the causes of "loss of skin color" in 144 patients, who visited Vitiligo Clinic of Kyoto University Hospital between April 2005 and August 2008. The numbers of patients with generalized and segmental Vitiligo vulgaris were 98 (68.1%) and 26 (18.1%), respectively. Small numbers of the patients suffered from Vogt-Koyanagi-Harada disease, piebaldism, congenital albinism, Hypomelanosis of Ito, post-inflammatory hypopigmentation, white leaf-shaped macules associated with tuberous sclerosis and nevus hypopigmentosus. One forth of the patients with generalized vitiligo had complications, while no complications were found in the patients with segmental vitiligo. Among the complications, autoimmune diseases dominated 43% (10 of 23 cases). Autoimmune thyroid diseases explained for the most of the complicated autoimmune diseases and were associated with 7.4% of the patients with generalized vitiligo. Minor autoimmune complications include myasthenia gravis, Sjogren syndrome and autoimmune nephritis. Reflecting the condition that our clinic is located in a university hospital, vitiligo patients with end-stage non-melanoma cancers of internal organs accounted for 8.4% of the patients of generalized vitiligo.

Introduction

Vitiligo vulgaris is an acquired, non-contagious disorder. Patients with vitiligo vulgaris visit a dermatology clinic complaining of "loss of skin color". However, white lesions are not always due to vitiligo vulgaris. This means that "loss of skin color" needs numerous differential diagnoses. In the present report, we reviewed the patients who visited our vitiligo clinic in Kyoto University Hospital. The differential diagnoses included numerous diseases. In addition, we also analyzed the complications of patients with vitiligo vulgaris in view of the autoimmune diseases.

Results

The causes of "loss of pigmentation from skin" were summarized in Table 1. The numbers of patients with generalized and segmental Vitiligo vulgaris were 98 (68.1%) and 26 (18.1%), respectively. This means that 86% of the patients complaining of "loss of skin color" were vitiligo vulgaris. Male/female ratios of generalized and segmental vitiligo were 1:1 and 2:1, respectively. Small numbers of patients complaining of "loss of skin color" suffered from Vogt-Koyanagi-Harada disease, piebaldism, congenital albinism, Hypomelanosis of Ito, post-inflammatory hypopigmentation, white leaf-shaped macules associated with tuberous sclerosis and nevus hypopigmentosus (see Table 1). The age of onset of generalized vitiligo was 42.3 years old (from two months old to 76 years old), which distributed uniformly in all ages, although 81% (21 of 26 cases) of patients with segmental vitiligo developed under the age of 30 and 58% had onset under the age of 20 (Table 2). In the 80% of patients with generalized vitiligo, at least one of the lesions of vitiligo existed in the sun-exposed areas, such as the face, neck or hand, which reflected their concern for public attention.

The cutaneous distribution of segmental vitiligo showed preference on the face. Twenty-one cases (84.6%) with segmental vitiligo developed in the face, including 11 cases in the region of the first branch of the trigeminal nerve (V1), 5 cases in the second branch (V2) region, 4 cases in the third branch (V3) region and 2 cases in both V1 and V2 regions (Table 2).

As for the complications associated with vitiligo, one forth of the patients with generalized vitiligo had complications, while the patients with segmental vitiligo were otherwise healthy (Table 4). Among the complications, autoimmune diseases dominated 43% (10 of 23 cases). Autoimmune thyroid diseases explained for the most of the complicated autoimmune diseases and were associated with 7 cases (7.4%) of the 98 patients with generalized vitiligo. These included 2 cases with Graves' disease (1 male and 1 female) and 5 cases with Hashimoto disease (2 male and 3 female). Minor autoimmune complications include myasthenia gravis (1 case), Sjogren syndrome (1 case) and autoimmune nephritis (2 cases). Reflecting the condition that our clinic is located in a university hospital, vitiligo patients with end-stage non-melanoma internal malignancies occupied 8 cases (8.4%) of the 98 patients of generalized vitiligo. However, we could not find any direct relations between vitiligo and the origins of the cancers, because complicated cancers included various kinds of origins, such as liver, stomach, prostate or thyroid.

Discussion

In the present report, we have reviewed the details of the patients whose main complaints were "loss of skin color". The differential

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Table 1 **The causes of "loss of pigmentaion from skin"**

Diseases	Number of cases (%)
Generalized vitiligo vulgaris	98 (68.1%)
Segmental viltiligo vulgaris	26 (18.1%)
Postinflammatory hypopigmentation	4 (2.8%)
Vogt-Koyanagi-Harada disease	2 (1.4%)
Vitiligo associated with malignant melanoma	2 (1.4%)
Piebaldism	2 (1.4%)
Congenital albinism	2 (1.4%)
Halo nevus	2 (1.4%)
Pityriasis simplex	2 (1.4%)
Hypomeanosis of Itoh	1 (0.7%)
White leaf-shaped macules associated with tuberous sclerosis	1 (0.7%)
Nevus depigmentosus	1 (0.7%)
Senile leukoderma	1 (0.7%)
Total	144 (100%)

Table 2 **Age of onset of generalized and segmental vitiligo**

Age of onset	Generalized number of cases (%)	Segmental number of cases (%)
0–10 y.o.	9 (9.2%)	7 (26.9%)
11–20 y.o.	12 (12.2%)	8 (30.8%)
21–30 y.o.	11 (11.2%)	6 (23.1%)
31–40 y.o.	14 (14.3%)	2 (7.7%)
41–50 y.o.	8 (8.2%)	0 (0%)
51–60 y.o.	14 (14.3%)	2 (7.7%)
61–70 y.o.	20 (20.4%)	1 (3.8%)
71–80 y.o.	10 (10.2%)	0 (0%)
Total	98 (100%)	26 (100%)
Average	42.3 y.o.	21.2 y.o.

Table 3 **The cutaneous distribution of segmental vitiligo**

Regions	Number of cases
V1	11 (42.3%)
V2	5 (19.2%)
V3	4 (15.4%)
V1 and V2	2 (7.7%)
Upper arm	2 (7.7%)
Chest	1 (3.8%)
Lumber	1 (3.8%)
Total	26 (100%)

V1 means a region of a first branch of the trigeminal nerve.

Table 4 **Complications associated with vitiligo**

Complication	Generalized (%)	Segmental (%)
Autoimmune thyroid diseases	7 (7.4%)	0
Halo nevus	2 (2.1%)	0
Autoimmune nephritis	2 (2.1%)	0
Myasthenia gravis	1 (1.1%)	0
Sjogren syndrome	1 (1.1%)	0
End-stage non-melanoma internal malignacies#	8 (8.4%)	0
malignant melanoma	2 (2.1%)	0
Total	23/98 (23.5%)	0/26 (0%)

#included 3 cases of liver cancer, 2 cases of breast cancer, 1 case of prostate cancer, gastric cancer and thyroid cancer.

diagnoses included numerous kinds of acquired and congenital skin diseases shown in the present report. We realized the diversity of the causes of "loss of skin color". In fact, we usually could find no clinical differences in the depigmented skin lesions between vitiligo vulgaris and the other diseases. Extensive physical and blood examinations were often required for making the exact diagnosis of "loss of skin color".

The lesions of segmental vitiligo in the present study showed a trigeminal distribution and developed among children and adolescents generalized vitiligio (Table 3). A previous review reported that segmental vitiligo develops before the age of 30 and the trigeminal dermatomes are the most commonly involved region[1]. Segmental lesions on the face are usually refractory to various kinds of therapies except for skin transplantation.[1] Therefore, we usually introduce camouflage for these young patients with segmental vitiligo.[2,3]

It was previously reported that there is an epidemiological association between generalized vitiligo and other autoimmune diseases. Several studies showed that vitiligo has been associated with autoimmune thyroid diseases, pernicious anemia, Addison's disease.[4-8] Also, in the present study, autoimmune thyroid diseases were found in 8.4% of the patients with generalized vitiligo, although no patients suffered from pernicious anemia or Addison's disease. This percentage is significantly higher than 1.90% frequency of autoimmune thyroid disease in the general United States population and is similar to 17.0% frequency among unselected white probands with vitiligo.[9,10] One female case with generalized vitiligo had a complication of myasthenia gravis and her titers of anti-acethylcholine-receptor antibody showed a parallel relation with her activity of generalized vitiligo. However, A few reports stated that simultaneous vitiligo and myasthenia gravis represented a coexistence rather than existence by accident because of a low frequency (0.5%) of vitiligo in patients with myasthenia gravis, compared with pemphigus and alopetia areata, which have an apparent relationship with myasthenia gravis.[11-13]

As for genetic aspects of vitiligo, several vitiligo susceptibility genes were identified.[14] Among them, general autoimmunity susceptibility genes such as cytotoxic T lymphocyte antigen 4 (CTLA-4),[15] protein tyrosine phosphatase, non-receptor type 22 (PTPN22),[16] the autoimmune regulator (AIRE)[17] and NACHT leucine-rich-repeat protein 1 (NALP1),[18] have been reported to have an association with vitiligo, because these genes play an important role to control autoimmune responses through regulatory T cells (Treg). In addition, accumulating evidence supports the idea that, in cancer-bearing patients, Treg suppresses anti-cancer immunity, which results in

tumor growth.[19] A recent study showed that Treg-specific CTLA-4 deficiency produces potent tumor immunity in mice.[20] The fact that, in the present study, 8.4% of the patients with generalized vitiligo have internal malignancies might reflect the disturbance of control of autoimmune response by Treg in patients with cancers.

Materials and Methods

Subjects. One hundred and forty-four patients, who visited VIliligo Clinic in Kyoto University Hospital between April 2005 and August 2008, were analyzed in this study. Their main complaint was "loss of pigmentation from skin". They gave us informed consents to this study. The Medical Ethics Committee of Kyoto University approved this work that was conducted in accordance with the Declaration of Helsinki principles.

Screening for autoimmune thyroid diseases. On the first visit of a patient with vitiligo vulgaris, physical examination of the neck and blood tests including complete blood cell count, routine chemistry, anti-nuclear antibody and free T3, free T4 and TSH, were performed. When an abnormal finding was detected, we planned more examinations in cooperation with endocrinologists. Intensive examinations included echogram of the neck and detection of anti-thyroid antibodies.

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