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Case report

Vitiligo in Croatia: A Case Report

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ABSTRACT

Vitiligo is an acquired, chronic, multifactorial disorder which involves complex interactions between genetic risk factors and environmental triggers. It is characterized by scattered circumscribed depigmented macules and patches anywhere on the skin that result from loss of functional melanocytes. According to our statistical data, 1.6% of the general population in Croatia suffers from vitiligo, but varies based on region. It affects all age groups equally, with female patients being more affected (53.95%) than male patients, and no difference in severity of vitiligo. We present a case of a sudden onset of vitiligo vulgaris from a female patient in her twenties, treated at the Department of Dermatology and Venereology. Her 12-year-old brother simultaneously developed acrofacial vitiligo, six months after their mother died in a car accident. She has been previously diagnosed with type I diabetes and autoimmune endocrinopathies. The depigmented patches covered approximately 60% of her body, with Koebner response on trauma. Although no characteristic UV fluorescence was detected on the affected area, histopathological and immunohistochemical analyses revealed a complete loss of melanocytes, while Langerhans` and dermal dendritic cells replaced the DOPA-positive melanocytes. TSH levels were elevated, and the ultrasound showed thyroid enlargement, which substantiated for a hypothyroidism therapy. Treatment by systemic corticosteroids for a 6 month period was successful in stabilizing the disease.

Key words: *pigmentation disorders, melanocytes, vitiligo, case*

Introduction

Vitiligo is an acquired chronic disease characterized by depigmented macular patches due to loss of epidermal melanocytes[1,2]. According to our statistical data, it affects 1.6% of the general population in Croatia. Female patients are more affected (53.95%) than male patients, with no difference in severity of vitiligo. Although most of our admitted patients have been in generally good health, vitiligo vulgaris is associated with a number of other autoimmune diseases, such as autoimmune thyroid disease, diabetes mellitus, pernicious anemia, rheumatoid arthritis, and lupus erythematosus. The localized form of vitiligo most frequently affects 21 to 28-year-old patients, while generalized form prevails in the age group from 29 to 36 years. Patients older than 77 years of age are very rarely affected. The most common localized type was focal (93.28%), and the most common generalized type was vitiligo vulgaris (53.7%). Most of our patients were admitted in September, probably due to increased contrast between involved and uninvolved skin during prolonged sun exposure. Most patients attribute the onset of their disease to specific life events (physical injury, emotional distress, illness or pregnancy).

The aim of this case report was to present our patient suffering from vitiligo vulgaris, and to evaluate clinical presentation, diagnostic and therapeutic difficulties for this condition.

Case Report

A 23-year-old Caucasian female patient was admitted to the University Hospital Center »Sestre milosrdnice«, in September 2010, due to prominent, generalized depigmented patches.

The disease began acutely, »over night« (in patients` own words), and progressed in the following order: dorsal aspects of hands, upper extremities, trunk, face and lower extremities. Within a few weeks 60% of her body was affected.

On admission to the hospital her height was 175 centimeters and weight was 60 kilograms, and the body mass index was normal (19.6). She was Fitzpatrick's phototype II.

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The affected area had no associated scaling. There was a lack of cutaneous induration or sclerosis. Skin lesions were asymptomatic and lacked clinical sings of inflammation. During dermatological examination leukotrichia of the occipital area was found. There was no mucosal involvement. She was without any subjective difficulties (e.g. pain, fever, weight loss).

There was a family history for this disorder; patient's 12-year-old brother has acrofacial vitiligo. The disease appeared almost simultaneously in both siblings. The onset of disease was attributed to emotional stress; after their mother had died in a car accident 6 months earlier, patient noticed the first lesions of vitiligo. She also noticed new depigmented lesions in sites of physical injury (Koebner phenomena).

The history of chronic sun exposure was negative. She was a non-smoker.

Illumination with Wood`s lamp showed no fluorescence of affected depigmented skin.

Vitiligo vulgaris has been diagnosed based on the clinical picture and pathohistological appearance. On admission, excisional biopsy of depigmented and non-lesional skin was performed.

Histopathological analysis of lesional skin has shown characteristic histologic features of vitiligo, such as total loss of melanocytes of the basal layer of the epidermis. Collagen fibers were not affected. There was no epidermal alteration or cellular infiltrate. Immunohistochemical analysis revealed the absence of melanocytes, without DOPA-positive melanocytes, which appear to be replaced by Langerhans` and dermal dendritic cells.

The diagnostic and laboratory tests have been performed during hospitalization. Obtained findings were within normal limits. Obtained echocardiogram and abdominal ultrasound were without significant changes. Ocular fundus on ophthalmological examination showed absence of depigmented lesions. She had no hearing problems.

Serology for Borrelia burgdorferi in our patient was negative.

Cytomegalovirus serology and Epstein-Barr virus specific serologies were negative. Serum level of tumor markers (CA 19-9, CEA, CA 125, CA 15-3, and CYFRA 21-1) was normal as well. HLA typing was positive for HLA A2, B51, B62, DR11, DR13, DR52, DQ1 and 3. In addition, our patient had autoimmune endocrinopathies; type I, insulin-dependent diabetes was diagnosed when she was 10 years old.

A serum thyroid-stimulating hormone (TSH) level and antithyroperoxidase antibodies were elevated, while T4 level was low. Additional laboratory findings include antithyroglobulin antibodies were within normal range. Ultrasound imaging of the thyroid gland revealed diffuse enlargement of the thyroid gland, so she was started on levothyroxine for hypothyroidism.

Results

Oral mini-pulse corticosteroid therapy (prednisolone) for 6 months has shown the ability to stabilize the disease with no exacerbations.

Topical class III corticosteroids were used for depigmented patches on her arms twice daily for two months, resulting in several perifollicular repigmentations. She had developed several side-effects such as atrophy and telangiectasiae. Topical 0,1% tacrolimus ointment was used for face and intertriginous areas twice daily for two months, but with no apparent success.

Narrow-band UVB was applied for six months with the total of 48 exposures. The starting dose was 250 mJ/cm^2, with 10% increments at each subsequent exposure. Treatment was administered two times per week but never on two consecutive days. Following the aforementioned therapeutic scheme, neither perifollicular repigmentation nor repigmentation from the periphery was detected.

Discussion and Conclusion

Vitiligo is an acquired, common, chronic disorder characterized by scattered circumscribed depigmented macules and pathes which vary in number and size[3].

Based on distribution, vitiligo is classified as: localized comprising unilateral depigmented macules following segmental (dermatomal) or focal pattern; generalized comprising acrofacial pattern involving face and distal extremities; and vitiligo vulgaris with widespread, usually symmetrically distributed lesions; universal vitiligo with complete or nearly complete depigmentation, and mucosal vitiligo presenting with typical depigmented macules exclusively on mucosal surfaces[4,5].

Our 23-year old female patient was diagnosed with generalized vitiligo, the most frequent type, based on the clinical presentation, history and histopathological findings. Occurrence of vitiliginous lesions within the areas of physical trauma or friction, known as Koebner phenomenon in vitiligo patients has been well described in literature and was also documented in our patient[6]. Occasionally there are circumscribed areas of white hair known as leukotrichia such as found in occipital region in our case[1,7]. Other potential associated findings include prematurely gray hair and audiovisual disturbances, which we did not find[1,5]. Skin and/or mucosal lesions are usually asymptomatic and gradually progress to involve larger areas, with unpredictable course and extent of skin/mucosal involvement[4]. Halo nevi may precede vitiliginous skin lesions, or may be found concomitantly[1,5]. At admission to our Department the patient had one halo nevus in her right scapular region.

Consistent with our histopathological findings, there is absence of melanocytes and inflammatory infiltrate in fully developed vitiligo lesions, although superficial dermal perivascular and perifollicular lymphocytic infiltrate may be detected at the margin of lesions in early lesions[8]. On electron microscopy, which was not performed in our case, absence of melanocytes and melanosomes in keratinocytes is documented[1]. Despite straightforward clinical appearance of vitiligo in majority of cases, several additional diagnostic procedures may be needed for confirmation of diagnosis in some less clear cases. Patients with

vitiligo should be examined under both visible and ultraviolet light of about 365 nm wavelengths (i.e. Wood`s lamp) in order to exclude tinea versicolor (varietas alba)[1].

Vitiligo can also resemble macules in idiopathic guttate hypomelanosis (IGH), pityriasis alba, postinflammatory hypopigmentation, chemical leukoderma, leukoderma associated with melanoma, sarcoidosis, hypomelanosis of Ito, nevus anemicus, piebaldism, leprosy, Vogt-Koyanagi-Harada syndrome and Waardenburg syndrome[1,5].

The important entities in differential diagnosis for vitiligo are also lichen sclerosus et atrophicus, congenital hypomelanotic macules of tuberous sclerosis, and hypopigmented mycosis fungoides. Excisional biopsy of perilesional skin should be performed[1,5].

According to the epidemiological data, vitiligo has a worldwide prevalence of 0.1–2%, equally affecting both sexes[5,8]. Croatian statistical data is within this range with female patients being overpresented. An apparent female predominance is probably the result of heightened perception of a cosmetic problem. Although vitiligo may appear at any age, from shortly after birth to late adulthood, most studies report that the average age of disease onset is 18–30 years of age, consistent with our patient's age[9–11].

Vitiligo is a multifactorial disorder, therefore, several hypotheses regarding the etiopathogenesis of vitiligo exist. The importance of genetic background is supported by studies demonstrating significantly higher (7–10 times) incidence of vitiligo among first degree relatives. Familial occurrence of vitiligo is present in approximately 20% of cases and is characterized by polygenic, non-Mendelian inheritance with incomplete penetrance and multiple susceptibility loci. Notably, studies suggest earlier onset of disease in familial vitiligo as opposed to non-familial, so our case report reflects those from the literature[12]. Certain HLA types have been frequently associated with vitiligo worldwide, primarily HLA A2 also found in our case, DR4, DR7 and Cw6[1,14].

Emotional stress, such as death of a close relative or other psychological trauma of similar intensity is a well-documented trigger of vitiligo in susceptible patients, just as described in our patient whose parent's death had been followed by appearance of vitiligo in her and her brother[15]. Numerous studies demonstrate that mental stress can directly and/or indirectly influence the survival and structural integrity of melanocytes[15,16]. Neurogenic factors influenced by mental stress, such as neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), catecholamines, and nerve growth factor (NGF), lead to melanocyte destruction[15].

Several comorbidities have been associated with vitiligo; among them the most frequent are autoimmune diseases such as thyroid-related disorders (Hashimoto's or Graves's disease), followed by psoriasis, diabetes mellitus type I, rheumatoid arthritis, alopecia areata, inflammatory bowel disease and systemic lupus erythematosus[17]. Our patient had been previously diagnosed with diabetes mellitus type I. Following laboratory workup, elevated thyroid-stimulating hormone (TSH) level was detected and thyroid gland enlargement was revealed on ultrasound imaging. These findings were consistent with Hashimoto's thyroiditis, as confirmed by endocrinologist's examination. Positive family history for Hashimoto's thyroiditis was obtained, involving the patient's deceased mother who had been diagnosed with this autoimmune disease. Of note, some suggestions have been made in the literature that individuals from families with an increased prevalence of thyroid disease, vitiligo and diabetes mellitus have increased risk for development of vitiligo[17]. Recently published study displayed evidence that non-segmental vitiligo associated with autoimmune thyroid disease in comparison with vitiligo without autoimmune thyroid disease has distinct clinical features consistent with our findings; female sex, greater body surface involvement, longer duration of disease and family history of autoimmune thyroid disease. It is therefore suggested that these patients should be monitored for thyroid disease[18]. Antinuclear antibodies, frequently found in vitiligo patients, were not detected in our patient's serum[9]. Among other conditions associated with vitiligo, low serum levels of 25-hydroxy vitamin D or frank vitamin D deficiency is also observed[19]. Interestingly, higher Fitzpatrick skin phototypes seem to correlate with lower serum 25-hydroxy vitamin D levels and a greater risk for vitamin D deficiency[19]. Although there has been no correlation concerning serum vitamin D levels and severity of vitiligo, it has been observed that patients with very low levels of serum vitamin D (<15 ng/mg) have substantially increased risk for another autoimmune disease, predominantly systemic lupus erythematosus, Sjögren's syndrome, Hashimoto's thyroiditis, Graves' disease, alopecia areata and inflammatory bowel disease[19]. In our case serum vitamin D level was within normal range.

Inspite of many different theories about the etiopathogenesis of vitiligo, its cause remains unknown, although evidence confirming autoimmune mechanisms have gained the most attention so far. Therefore, treatment modalities remain limited, whereas treatment approach is preferentially individualized and polyvalent. In our case, success of treatment including systemic and topical corticosteroids, topical calcineurin inhibitor and narrow-band phototherapy was modest, accompanied by diminished patient compliance and satisfaction[20]. Another possible approach for patients with >50% of skin involvement is to consider depigmentation techniques using hydroquinone monobenzyl ether or 4-methoxyphenol alone or in combination with Q-switched ruby laser[4]. This approach has not been tried on our patient yet.

A universal treatment for vitiligo remains to be discovered. Taking our results into account and after reviewing recently published literature on this topic, we would like to accentuate the need for more comprehensive approach to vitiligo in the future. More precise definitions of various vitiligo subtypes should be obtained. Disease severity, progression and duration should also be implemented into these variables. Each treatment should be individualized and several treatment modalities should be applied simultaneously. Treatment outcome should be evaluated by re-

pigmentation and its maintenance, cosmetic acceptability, quality of life, stabilization of vitiligo and adverse effects of therapy. With these requests fulfilled, perhaps some future studies of vitiligo and its treatment modalities could be more unifying, clear, easily interpreted and applicable to our everyday practice.

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VITILIGO U HRVATSKOJ: PRIKAZ SLUČAJA

SAŽETAK

Vitiligo je stečena, kronična, multifaktorijalna bolest koja predstavlja složeno međudjelovanje genetičkih i okolišnih rizičnih čimbenika. Klinički se bolest očituje pojavom diseminiranih, depigmentiranih makula i areala na koži bilo kojeg dijela tijela kao posljedica gubitka funcionalnih melanocita. Prema statističkim podacima, 1,6% opće populacije Republike Hrvatske boluje od vitiliga, incidencija varira ovisno o geografskom području. Podjednako zahvaća sve dobne skupine, češće žene (53,95%), bez razlike u težini kliničke slike. Predstavljamo slučaj bolesnice kod koje se akutno razvio vulgarni vitiligo, te je primljena i liječena u našoj Klinici za kožne i spolne bolesti. Gotovo istovremeno, njezin 12-o godišnji brat je razvio akrofacijalni oblik vitiliga, šest mjeseci nakon što je njihova majka nastradala u prometnoj nesreći. Prethodno joj je dijagnosticiran dijabetes tip I uz ostale autoimune endokrinopatije. Depigmentirani areali su zahvatili približno 60% površine tijela, uz pozitivan Koebnerov fenomen. Iako nije uočena karakteristična UV fluorescencija na obuhvaćenom području, patohistološke te imunohistokemijske analize su otkrile potpun gubitak melanocita, dok su DOPA-pozitivni melanociti zamijenjeni Langerhansovim stanicama i dermalnim dendritičkim stanicama. Razina TSH je bila povišena, a ultrazvučnim pregledom je uočena uvećana štitnjača, što je rezultiralo uvođenjem nadomjesne terapije za hipotireozu. Liječenje sistemnim kortikosteroidima u periodu od 6 mjeseci uspješno je stabiliziralo bolest.