Premature ovarian failure and thyroid anomalies in patients with autoimmune disturbances

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Abstract

Premature ovarian failure is associated with many other autoimmune diseases. We report 3 cases reports in this paper associating thyroid autoimmune disease, and at least 1 more autoimmune pathology. A 45-year female is diagnosed at age of 42 with acute adrenal insufficiency, Hashimoto's thyroiditis induced hypothyroidism, secondary amenorrhea (follicle-stimulating hormone (FSH) of 18 mUI/ml), and osteoporosis. Adrenal and thyroid substitution was started, and intravenously zoledronic acid. Within 6 months, the thyroid stimulating hormone normalized, and the menses re-started. A 64-year female has premature ovarian failure since age of 40, autoimmune hypothyroidism since age of 54, psoriasis vulgaris, and osteoporosis since the age of 53. Raloxifene was used for 3 years then Dual-energy X-ray Absortiometry pointed osteopenia that was conserved up to the present. A 53-year female with menopause since age of 40 is treated for autoimmune hypothyroidism, while scleroderma was diagnosed. Later esofagitis developed, as well as osteopenia. FSH was not as high as expected for ovarian insufficiency in case 1, suggesting a second mechanism of hypothalamic origin based on consumptive syndrome in severe glucocorticoids deficiency. Transitory secondary amenorrhea is an argument that re-balancing the general biochemical and endocrine parameters, might improve the ovarian function. The cases 2 and 3 had untreated premature ovarian failure but the therapeutic opportunity window was lost at the moment of admission. The skin lesions as psoriasis or sclerodermia are a marker of severity. We highlight the importance of autoimmune clusters including the thyroid pathologies in females underlying premature ovarian failure. We also encourage the routine bone mineral density check since menopausal osteoporosis/osteopenia might be already presented.
Keywords: *premature ovarian failure, autoimmune thyroiditis, osteoporosis, type 2 polyglandular autoimmune syndrome, psoriasis, sclerodermia*

Introduction

Premature ovarian failure embraces a large number of causes and it has an increasing frequency over the last years. Various endocrine aspects should be considered. Autoimmune polyglandular syndromes are a rare combination of diseases, and the adult type, also known as type 2 includes at least two autoimmune diseases, especially adrenal insufficiency or autoimmune thyroiditis. The spectrum of endocrine anomalies is extremely different and the premature ovarian failure might be seen. Specific genetic test are not usually used[(1)].

In this paper our aim is to present a series of three cases with premature ovarian failure and thyroid autoimmune disease. One case had transitory secondary amenorrhea until the adrenal and thyroid insufficiency was corrected, and the other two cases presented with dermatologic and rheumatologic lesions at the moment when the patients were admitted for endocrine evaluation. In their medical history, we noticed untreated premature ovarian failure. All the patients have given their informed consent.

Cases report

Case 1

T.D. 45-year old female has negative family history. At age of 42 years she was first admitted on "C.I.Parhon" National Institute of Endocrinology, from Bucharest, Romania. She presented collapse, progressive skin hyperpigmentation in the last several weeks and secondary amenorrhea in the last six months. On admission, acute adrenal insufficiency was sustained based on high adrenocoticotropic hormone levels of 1250 pg/mL (with normal levels below 66 pg/mL). Intravenous glucocorticoid therapy was introduced as an emergency in a life threat situation, and then continued with oral daily prednisone of 7.5 mg. In the same time, Hashimoto's thyroiditis was diagnosed based of the anti-thyroid peroxidase antibodies of 972 UI/mL (with normal levels under 30 UI/mL), and hypothyroidism based of a high thyroid stimulating hormone (TSH) level of 9.2 microUI/mL (with normal levels less than 5 microUI/mL). Levothyroxine therapy was introduced after the cardiovascular parameters normalization. The follicle-stimulating hormone (FSH) level was of 18 mUI/ml. Osteoporosis was diagnosed based on central Dual-energy X-ray Absortiometry (DXA) assessment (Table 1). She was treated with 15 mg intravenously zoledronic acid associated with vitamin D and calcium. Within six months, the TSH decreased to 1.5 microUI/mL, and the menses re-started without any specific therapy. She felt well under adequate therapy for chronic adrenal

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Table 1 Central DXA (Dual X-Ray Absortiometry) in a female with adrenal crisis, autoimmune hypothyroidism and secondary amenorrhea

Central DXA			
Age of 42 years	**Lumbar L1-4**	**Femoral neck**	**Total hip**
BMD (g/cm^2)	0.754	0.637	0.717
T-Score	-3.5	-2.9	-2.3
Z-Score	-3	-2	-1.7
Age of 43 years	**Lumbar L1-4**	**Femoral neck**	**Total hip**
BMD (g/cm^2)	0.806	0.733	0.770
T-Score	-3.1	-2.2	-1.9
Z-Score	-2.9	-1.5	-1.5
Age of 44 years	**Lumbar L1-4**	**Femoral neck**	**Total hip**
BMD (g/cm^2)	0.819	0.699	0.774
T-Score	-3	-2.4	-1.9
Z-Score	-2.5	-1.6	-1.2

insufficiency and hypothyroidism. The bone mineral density (BMD) increased under yearly zoledronic acid at age of 43 and 44 years (Table 1). The menses remained regular up to present.

Case 2

B.L. 64-year female, with negative family history, is known with premature ovarian failure at age of 40 without therapy, and also autoimmune hypothyroidism since the age of 54 under levothyroxine therapy. She has persistent lesions of psoriasis vulgaris, as well as osteoporosis since the age of 53 years, based on a T-Score at lumbar DXA of -3.2 (BMD of 0.818 g/cm^2, and a Z-s of -3) (Figure 1). She was treated with weekly raloxifene associated with vitamin D and calcium supplements for three years, and then DXA pointed an osteopenia lumbar T-Score of -2.4 (BMD of 0.911g/cm^2, and Z-Score of -2.1). The osteopenia score was conserved up to the age of 64 years, under vitamin D and calcium supplements. Thus, the patient had a combination of autoimmune diseases: premature ovarian failure (most probably of autoimmune cause), autoimmune hypothyroidism, and psoriasis.

Case 3

I.R., 53-year old female, with irrelevant family history, has the following medical history: she entered menopause at age of 40 and she did not received any medical therapy for this matter. At age of 49 years she was first admitted on "C.I. Parhon" National Institute of Endocrinology", from Bucharest, Romania for a suspicion of hypothyroidism. This was confirmed (i.e. by a TSH level of 10 microUI/mL), and a high level of anti-thyroid peroxidase antibodies was presented (of 42 UI/mL, with normal level of less than 30 UI/mL). Hashimoto's thyroiditis was confirmed and levothyroxine therapy was started. She showed carotene skin and hypomimia that first was considered a myxedema but while TSH was corrected under adequate therapy, the skin anomalies remained unchanged (Figure 2). A scleroderma was suspected, and then confirmed by rheumatologic evaluation. Later esofagitis was found, as well as osteopenia at DXA based on a T-Score of -1 at the level of femoral neck (a BMD of 0.9 g/cm^2, and Z-Score of -0.8). The patient was followed up until present.

Discussions

The series of these cases introduces the idea of premature ovarian failure as a component in polyglandular autoimmune syndrome. In a study of 258 patients with Addison's disease a 20% of them associated premature ovarian failure[1,2]. The steroidogenic antibodies are useful for the second one, and predict the ovarian failure if the patient had adrenal insufficiency. Nevertheless, as in our first case, the usual check up of these antibodies is not necessary[2]. Remarkably, in this situation, the FSH was not as high as expected for ovarian insufficiency, suggesting the idea of a second mechanism of hypothalamic origin based on consumptive syndrome in severe glucocorticoids deficiency. Moreover, the transitory aspect of the secondary amenorrhea is an argument that re-balancing the general biochemical and endocrine parameters, might improve the ovarian function. The first case it also should be considered for the particular onset with adrenal crisis in an autoimmune constellation of diseases that marks the severity of the syndrome[3]. The case number 2 and 3 had a medical history of premature ovarian failure that was not treated at the moment of diagnosis, and the patients were admitted several years later when hormonal therapy was no longer indicated. All

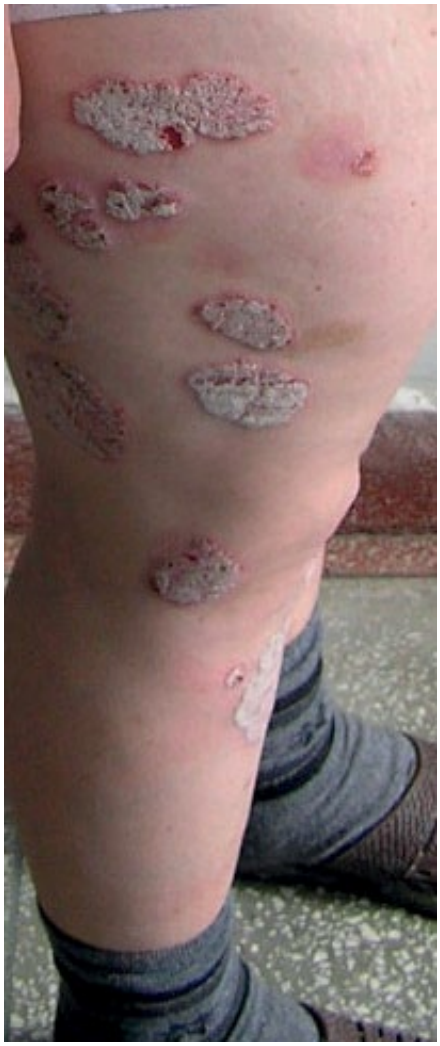

Figure 1. Psoriasis in a female with autoimmune hypothyroidism and premature ovarian failure

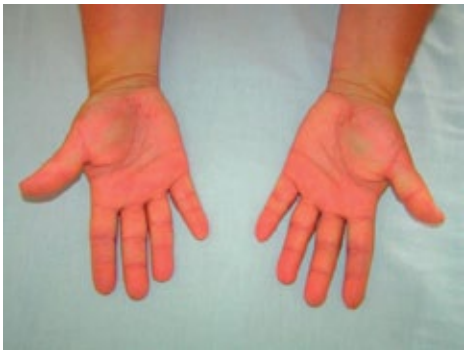

Figure 2. Carotene skin in a female patient with scleroderma, autoimmune hypothyroidism and premature ovarian failure

the three cases present, a part from premature ovarian failure, an autoimmune thyroiditis with hypothyroidism that made necessary adequate therapy. This was cited in association with skin autoimmune diseases as multiple sclerosis, vitiligo, psoriasis, systemic lupus erythematosus, and atopic eczema[4,5]. The skin lesions in psoriasis are a marker of severity of disease, and possible to the risk of another autoimmune disease[6]. The scleroderma was studied in relationship to autoimmune thyroid pathology of any kind and a longitudinal survey study indicated a higher risk in female patients, especially if TSH is increased or the thyroid antibodies positive, thus lifelong follow up is necessary[7]. Inversely, some authors consider that autoimmune hypothyroidism is the most frequent feature of type 2 polyglandular autoimmune syndrome[8].

In the cases we presented, the bone pathology was presented as osteoporosis or osteopenia. If premature hypogonadism is presented, this is one of the mechanisms. The link with autoimmune pathology is registered via cytokines as tumor necrosis factor α, as seen in rheumatoid arthritis[9]. As link between thyroid autoimmune disease and premature menopause or ovarian failure we considered the common or similar antibodies, also studies have shown that the actual age of menopause is not exactly correlated to thyroid diseases in case of appropriate therapy[10].

Conclusions

Starting from three cases presentations we would like to point out the importance of autoimmune diseases clusters in patients with premature ovarian failure, the thyroid having a central place in clinical check up. ■

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