CASE REPORTS

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Hypothyroidism and Addison's Disease Totally Corrected by Adrenal Replacement Therapy

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THE COEXISTENCE of multiple endocrinopathic conditions has been increasingly studied over the past ten years. When Gastineau and Arnold[1] reviewed 538 patients with Addison's disease, about 2 percent (11 cases) were noted to have had thyroid failure also. Two of these patients with mild clinical myxedema became euthyroid after adrenal replacement alone. One similar case was reported by Borghi.[2]

The patient described here had myxedema and Addison's disease concurrently. Subsequent adrenal replacement therapy alone corrected the hypothyroidism as well as the Addison's disease.

Report of a Case

The patient, a 44-year-old Caucasian woman nurse, was admitted to the hospital 15 November 1969 with a history of weight loss and progressive weakness over the past year. She had been sleeping 12 hours a night and awakened feeling tired. Nausea and anorexia developed and she had lost 30 pounds in the year before admittance. She ate mostly soups but did not crave salt. Cold intolerance had become pronounced recently, although the patient had had it to some extent for several years. Her axillary hair had become scant and she no longer needed to shave under her arms as she had done regularly before. She had menstrual periods but light flow. Libido had declined during the latter months of illness. Constipation had been a longstanding problem. She had had vitiligo about the eyes and vulva area for at least ten years; and recently she noticed increasing generalized brown pigmentation of her skin, making the areas of vitiligo more prominent by contrast. It is interesting that diabetes requiring insulin had recently developed in the patient's daughter, aged 16, although there was no known history of diabetes on either side of her family.

On physical examination the patient appeared chronically ill. She had gray, rather fine hair, a decided tan over the entire body with numerous dark freckles and areas of depigmentation about the eyes and vulva. She moved slowly and although she answered questions well, her responses were considerably delayed. Blood pressure was 90/70 mm of mercury recumbent, and 65/50 erect (with a "light-headed feeling"). The pulse was 76 and regular. Visual fields were intact by confrontation. No abnormality of mucous membranes were noted and there was no thyroid enlargement or tenderness, no cervical or other lymphadenopathy. The abdomen was normal to palpation. A right lower quadrant surgical scar (appendectomy at age 19) revealed no pigmentation. Heart sounds were distant and quiet. Peripheral pulses were weak. Except for the previously mentioned vitiligo about the vulva, pelvic examination was unremarkable. Muscle tone in the extremities was poor and veins were notably flat with limbs dependent. Results of neurological examination were essentially negative except for delay in the relaxation phase of the deep tendon reflexes and the already noted slowed response.

Laboratory studies

The blood cell count was remarkable in that there was relative lymphocytosis with 6,500 leukocytes per cu mm and a differential of 37 percent polymorphonuclear cells, 1 percent eosinophils, 4 percent monocytes and 58 percent lymphocytes.

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Results of urinalysis were within normal limits. Blood urea nitrogen was 23 mg per 100 ml. Serum electrolytes were: sodium 122, potassium 3.7, carbon dioxide 25, and chloride 89 mEq per liter. Blood cortisol at 9 a.m. was 4.6 mcg per 100 ml and at 8 p.m. was 4.8 mcg. Baseline 24-hour urine studies were as follows: 17-hydroxycorticosteroids, 0.4 mg per 24 hours, and 17-ketosteroids 2.1 mg per 24 hours.

An ACTH stimulation test was carried out for three days utilizing 25 units of ACTH in 500 ml of normal saline solution infused over an eight-hour period, and a 24-hour urine collection was completed for each day. The results: 17-hydroxycorticosteroid per 24 hours, 0.1 mg the first day, 1.2 mg the second day, and 1.4 mg the third day.

A water loading test was carried out as follows: the patient ingested 1,500 ml of water over a 45-minute period. A five-hour urine collection was then done, the patient putting out 550 ml.

An electrocardiogram showed low voltage in all leads. An x-ray film of the chest showed no evidence of pulmonary disease. The heart was noted to be remarkably small.

Thyroid studies included the following: Protein-bound iodine, 2.5 mcg per 100 ml; cholesterol, 240 mg per 100 ml; triiodothyronine, 27 percent (repeat 18 percent); tetraiodothyronine, 1.4 mcg per 100 ml (repeat 1.4); thyroid antibody, negative.

Results of glucose tolerance test (oral 100 ml glucose) was as follows: Fasting blood glucose, 82 mg per 100 ml; ½ hour 114 mg, 1 hour 146 mg, 2 hours 148 mg, 3 hours 138 mg and 4 hours 140 mg.

Skin tests were negative for tuberculin purified protein derivative intermediate, histoplasmosis, and coccidioidomycosis.

A Papanicolaou smear revealed a moderate estrogen effect.

Clinical course

After completion of baseline studies, cortisone was begun, 12.5 mg twice a day. A few days later fludrocortisone (Florinef®) 0.2 mg and sodium chloride 4.0 grams were added to the cortisone to improve the mineralocorticoid effect and replace the depleted blood volume. The patient's clinical response was slow and a loss of cortisone potency was suspected. She was switched to hydrocortisone, 10 mg three times a day. Gradually she improved with volume replacement and disappearance of postural hypotension and nausea. Her appetite increased and as her weight rose, slight edema developed. Hence, fludrocortisone was reduced to 0.1 mg daily and sodium chloride to 2 grams. She continued to improve, but at a slower rate than had been anticipated and was felt to be due to the thyroid deficiency. A month after the patient was admitted to hospital, tetraiodothyronine content had risen to 2.4 mcg per 100 ml and cholesterol had fallen to 185 mg per 100 ml, suggesting that the thyroid function was returning. A water loading test by the same method before was carried out and the five-hour urine collection was 1,200 ml. Electrolyte values had returned to normal (sodium 140, potassium 4.4, carbon dioxide 24 and chloride 104 mEq per liter). Shortly thereafter a fasting and two-hour postprandial blood glucose determination showed normal values —103 mg and 98 mg per 100 ml, respectively.

The patient's clinical status then continued to improve, with return of normal strength, disappearance of postural hypotension, clearing of persistent fatigue, increase in libido, return to previous weight, fading of brown pigmentation of the skin and increase in cold tolerance. She was able to carry on with her home, family, and full-time nursing duties. Results of thyroid function tests continued to improve. (See Table 1). A 24-hour radioactive iodine uptake and scan were

TABLE 1.—*Results of Thyroid Function Studies in Case Herein Reported*

		1969*						1970					1971
Test	*Normal Value*	11/16	11/21	11/29	12/1	12/4	12/15	1/5	1/16	1/19	3/21	9/10	6/29
PBI	3.5 to 8.0 mcg	..	..	2.8	..	..	..	..	4.8	4.6	..	..	..
T_4	3.0 to 7.3 mcg	..	1.4	..	1.4	..	2.4	3.6	3.0	..	3.9	4.0	4.9
T_3	25 to 35	..	27.0	..	18.0	..	..	28.0	29.0	..	..	29.0	..
IST_3	0.8 to 1.3	..	..	..	..	..	0.8	0.97	1.02	..	1.05	..	..
Cholesterol	150 to 260 mg	240	..	..	..	205	185	195	200	200	..	..	..

*Adrenal replacement therapy begun 11/27/69

PBI = protein-bound iodine; T_4 = tetraiodothyronine; T_3 = triiodothyronine; IST_3 = index of serum binding of T_3 (method developed at Solano Laboratories)

within normal limits. The scan was symmetrical and showed a normal sized gland.

At last report the patient's steroid dosage had been reduced slightly. She was taking hydrocortisone, 10 mg twice a day, and fludrocortisone (Florinef) 0.1 mg daily. She no longer required sodium chloride tablets, but used salt to taste with her regular diet.

Discussion

In this case the patient appeared clinically to have Addison's disease, and this was confirmed by laboratory studies. Hypothyroidism was somewhat obscured by the overwhelming signs and symptoms related to the adrenal insufficiency. The possibility of panhypopotuitarism was considered but ruled out on the basis of the presence of pronounced skin pigmentation and maintenance of menstrual periods.

Because the clinical progress was slow after adrenal replacement therapy was begun, thyroid replacement therapy was strongly considered. However, in light of the gradual apparent return of the thyroid function this was not done and in less than a year the patient's thyroid function returned to normal with only adrenal replacement therapy.

This phenomenon has been previously described by Gastineau and Arnold[1] in two cases. In one of their cases, diabetes developed as well. In the present case, the oral glucose tolerance test before treatment revealed a slow rise, with persistence of a slightly elevated blood glucose to four hours. This response probably reflected very slow gastrointestinal absorption due to her previously limited food intake and hypothyroidism, not a true diabetic state. Recently a fasting blood glucose and a two-hour post prandial blood glucose were normal. The presence of vitiligo, which preceded the endocrine problems, might suggest the development of a progression of autoimmune diathesis involving first the skin and then, later, the adrenal and the thyroid gland.

There are a number of possible explanations for reversal of this hypothyroid state associated with Addison's disease with no other treatment than adrenal replacement administration.

It is well known that in Addison's disease, lymphocytic infiltration occurs in the thyroid gland and other tissues.[3] Presumably if this infiltration is extensive enough, thyroid insufficiency might occur. However, hypothyroidism rarely does develop, suggesting that thyroid reserve is sufficient to maintain a euthyroid state in spite of compromise of the thyroid gland. Schmidt's syndrome[3] has been characterized by the occurrence of Addison's disease in association with chronic thyroiditis and atrophy of the thyroid gland, with lymphocytic infiltration of both the adrenals and the thyroid.[3] Subsequently in similar cases the patients were shown to have increased antiadrenal and antithyroid antibodies.[4] The patient in the present case did not have demonstrable thyroid antibodies. A test for adrenal antibodies was not done. The incidence of hypothyroidism and Addison's disease combined may be higher than the 2 percent discussed by Carpenter et al.[5]

Hydrocortisone replacement therapy for our patient's Addison's disease may have had a therapeutic effect on the thyroid gland through an anti-inflammatory effect on the "thyroiditis" and a reduction in the lymphoid hyperplasia and infiltration, with subsequent gradual resumption of normal thyroid activity. The replacement dose of hydrocortisone may have been adequate to suppress inflammation due to slowed metabolism and excretion of the glucocorticoid. Against this hypothesis would be the lack of history suggestive of thyroiditis, the fact that the thyroid gland was of normal size, the absence of inflammation, and the absence of thyroid antibodies.

Another theoretical explanation for this complex endocrinopathic condition could be central in nature. The anterior pituitary cells which produce ACTH and thyroid stimulating hormone (TSH) may be similar or the same.[7] There is some evidence to suggest that corticotropin may suppress TSH production.[6-8] In this patient ACTH levels, before treatment, would probably be very high due to lack of suppression by circulating cortisol. TSH levels might be extremely low due to suppression of TSH production by the ACTH, or if the cells which produce both tropic hormones are the same, production might be preoccupied with ACTH production and decreased TSH synthesis. With institution of hydrocortisone replacement therapy, ACTH production would be reduced, and TSH production would increase, with subsequent gradual "waking up" of the thyroid gland and appropriate thyroid hormone production. In a more recent report,[9] glucocorticoid administration resulted in reduction in plasma TSH concentration in both hypothyroid and normal human subjects. This observation would appear to be in conflict with the above observation. However, in the same report

it was noted that TSH rebound was observed in a high proportion of the subjects. They suggested that during glucocorticoid treatment when thyrotropin releasing factor (TRF) is presumably impaired, it could accumulate intracellularly in the appropriate hypothalamic centers. Subsequently, this accumulated TRF might be rapidly released and therefore briefly stimulate TSH secretion through its known pituitary action. Possibly in the present patient the rebound phenomenon with briefly higher than normal TSH levels resulted in adequate thyroid stimulation to resume thyroid function. TSH measurement or a TSH stimulation test would have been helpful in localizing possible sites of glucocorticoid effects on restoring the patient to a euthyroid state.

In a patient who exhibits clinical and laboratory evidence of Addison's disease and thyroid insufficiency, adrenal replacement therapy should be started and continued. The patient should be observed closely over subsequent weeks, particularly for complications of hypothyroidism; and if complications develop, gradual thyroid replacement should be initiated and maintained for two to three months. After that time the thyroid hormone could be discontinued for an appropriate period and thyroid status could be reevaluated for return of function. However if, as in the present case, the patient continues to show clinical and laboratory evidence of improved thyroid function, only adrenal replacement therapy is needed.

Summary

A case of Addison's disease associated with hypothyroidism which was corrected totally with only adrenal replacement therapy is presented. Several theoretical explanations for this phenomenon are discussed.

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Lupus Nephritis Complicated by Fatal Disseminated Coccidioidomycosis

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SYSTEMIC LUPUS ERYTHEMATOSUS, renal failure and steroid therapy are known predisposing conditions to opportunistic infectious disorders.[1-3] Among the fungal organisms causing such septic processes, Coccidioides immitis is relatively infrequent despite its classification as a "predominantly pathogenic" opportunistic fungus.[4,5] The following case report concerns a woman with end-stage lupus nephritis under treatment with corticosteroids and dialysis whose course was complicated by fulminant disseminated coccidioidomycosis. So far as we could determine, this is only the fourth patient described with lupus complicated by coccidioidomycosis[4,6,7] and the first for whom complete autopsy findings are available. A comparative description of the previous cases, the relationship to predisposing factors and the diagnostic difficulties in the current case are discussed.

Report of a Case

A 29-year-old woman was admitted to the Naval Hospital, Oakland, January 2, 1971, with uremia, hypertension and congestive heart failure. Ten years previously, while living in San Diego, the patient had had a post-partum cutaneous erup-

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