INTERNAL MEDICINE

□ CASE REPORT □

Werner Syndrome and Diabetes Mellitus Accompanied by Adrenal Cortex Cancer

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Abstract

Werner syndrome is a rare genetic disease characterized by progeria, diabetes mellitus, cataracts and various types of malignancy. However, there are few reports showing adrenal cortex cancer in subjects with Werner syndrome. We herein report an extremely rare case of Werner syndrome accompanied by adrenal cortex cancer. Based on the data obtained from blood samples, computed tomography, magnetic resonance imaging and ^{131}I adosterol scintigraphy, we diagnosed this subject with adrenal cortex cancer and Cushing's syndrome. Since the prognosis of adrenal cancer is very poor, we should be aware of the possibility of adrenal cancer occurring in subjects with Werner syndrome.

Key words: Werner syndrome, diabetes mellitus, adrenal cancer

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Introduction

Werner syndrome is a rare genetic disease inherited as an autosomal recessive trait and is characterized by progeria, diabetes mellitus, cataracts and various types of malignancy, especially non-epithelial tumors (1, 2). There are many mutations in the Werner syndrome gene, and most are associated with the pathogenesis of Werner syndrome (3). It has been also reported that the frequency of various types of malignancy is higher in subjects with diabetes mellitus than in those without (4, 5). Adrenal cortex cancer is a rare epithelial tumors, and in general, its prognosis is very poor (6, 7). Few reports have described adrenal cortex cancer in subjects with Werner syndrome and diabetes mellitus. We herein report an extremely rare case of Werner syndrome and diabetes mellitus accompanied by adrenal cortex cancer.

Case Report

A 55-year-old woman was hospitalized for the treatment of a refractory ulcer in the Achilles tendon that was likely due to Werner syndrome. She had been diagnosed with Werner syndrome and diabetes mellitus at 40 years of age. In her late forties, an ulcer was observed in the Achilles tendon and had not resolved over several years. Therefore, she was hospitalized at our institution.

On admission, her height was 144.1 cm, and her body weight was 37.8 kg (body mass index: 18.2 kg/m^2). Her blood pressure was 187/83 mmHg, and her heart rate was 99 bpm. Her body temperature was 36.5°C. Her hair was thin and pale brown. Her face was bird-like, and her voice was harmonic and hoarse, both of which were compatible with Werner syndrome. In addition, she had cataracts in both eyes. Her subcutaneous fat mass in the arms and legs was extremely small compared to that in the body trunk. HbA1c was 7.3% under treatment with oral anti-diabetic medicine (glimepiride 0.5 mg, sitagliptin 50 mg, metformin

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250 mg). Concerning diabetic complications in this subject, diabetic nephropathy (microalbuminuria) and mild peripheral neuropathy were observed, but diabetic retinopathy was not observed. There were no abnormalities in the electrolyte levels or the renal and liver function. There were also no apparent Cushing's symptoms. Moon face, buffalo hump and red skin striae were not observed.

In our department, we perform an endocrinological examination, such as adrenocorticotropic hormone (ACTH) and cortisol measurements, in all diabetic subjects on admission. At that time, cortisol was increased (21.2 mg/dL), and ACTH was suppressed (<1.0 pg/mL). dehydroepiandrosterone-sulfate (DHEA-S) was low (2 μg/dL), and while urinary cortisol was high (465 μg/day), urinary DHEA-S was undetectable. Based on these findings, we started to suspect the presence of Cushing's syndrome in this subject. Other endocrine hormone levels were within normal range. Daily variations in the cortisol level were not observed; cortisol and ACTH at 8:00, 10:00, 14:00, 20:00 and 23:00 were 19.6 μg/dL and <1.0 pg/mL; 26.2 μg/dL and <1.0 pg/mL; 17.8 μg/dL and <1.0 pg/mL; 16.9 μg/dL and <1.0 pg/mL and 14.7 μg/dL and <1.0 pg/mL, respectively. In addition, on the dexamethasone suppression test (1 mg, overnight), cortisol was not suppressed (cortisol 17.8 μg/dL, ACTH <1.0 pg/mL). These findings for the daily variation in the cortisol level and the dexamethasone suppression test were compatible with Cushing's syndrome. In serum steroid profiling using liquid chromatography/mass spectrometry (LC/MS), androgen secretion was not enhanced, suggesting that the cortisol system alone was accelerated in this subject. In addition, various tumor markers were within normal range.

After admission, we started intensive insulin therapy (a total of 12 units/day of ultra-fast-acting insulin) and obtained good glycemic control. Indeed, HbA1c was decreased to 6.6%. As shown in Fig. 1A, significant and segmented calcification was observed in the Achilles tendon, which was typical of Werner syndrome. Furthermore, during a preoperative examination of the ulcer, a right adrenal tumor was found. As shown in Fig. 1B, computed tomography (CT) revealed a neoplastic lesion. Its maximum diameter was approximately 8 cm, and inside, it showed a mosaic pattern, including a substantial ratio of low-density area. Magnetic resonance imaging (MRI) also showed a neoplastic lesion including high-density area due to calcification (Fig. 1C). Staining was delayed, and abnormal findings were observed in the right renal vein and inferior vena cava, suggesting the invasion of adrenal cancer. In ^{131}I adosterol scintigraphy, accumulation was not observed in the right adrenal tumor. Based on these findings, we diagnosed this subject with adrenal cortex cancer and Cushing's syndrome.

During the operation, invasion of adrenal cortex cancer into the right renal vein and inferior vena cava was confirmed. Therefore, right adrenalectomy, right renal vein reconstruction and inferior vena cava reconstruction were performed. As shown in Fig. 2A, the maximum diameter was 10.5 cm in the resected specimen, and the cut surface was solid and myxomatous. We ultimately definitively diagnosed this subject with right adrenal cortex cancer.

As shown in the upper and middle panels in Fig. 2B, dysplastic epithelium cells were observed on Hematoxylin and Eosin (HE) staining, indicating myxoid adrenocortical carcinoma. The nuclei were relatively small, and most of the cytoplasm was eosinophilic. Necrosis and capsular invasion were observed, although no abnormal mitoses were observed. Therefore, the modified Weiss' score was 4, and the tumor staging was stage III (T4, tumor invasive in adjacent organs; N0, no positive lymph nodes; M0, no distant metastases) (8, 9). These data suggest that the adrenal cortex cancer in this subject was highly malignant and that the prognosis was very poor. In addition, positive staining (brown) was observed on immunostaining for steroidogenic factor-1 (SF-1), a marker of adrenal cortex tumor (low panel in Fig. 2B). After the operation, there were no problems with steroid replacement (hydrocortisone 10 mg) or intensive insulin therapy (a total of 20 units/day of ultra-fast-acting insulin), although the HbA1c was increased to 7.5% due to the usage of hydrocortisone.

Discussion

It is well known that Werner syndrome is often accompanied by diabetes, and the concurrence of Werner syndrome and diabetes is not rare at all. Indeed, it has been reported that more than 60% of subjects with Werner syndrome have diabetes (10). In this report we described an extremely rare case of Werner syndrome and diabetes mellitus accompanied by adrenal cortex cancer that was successfully treated surgically. Since there have been few reports showing adrenal cortex cancer in subjects with Werner syndrome, this report calls attention to the fact that adrenal cortex cancer can be complicated by Werner syndrome.

Werner syndrome is a rare genetic disease often accompanied by various types of malignancy (1, 2). In addition, it has been reported that the frequency of various types of malignancy is higher in subjects with diabetes mellitus than in those without (4, 5). Therefore, we assumed that the presence of diabetes as well as Werner syndrome was involved in the initiation and/or progression of adrenal cortex cancer in this subject.

In our case, adrenal cortex cancer was successfully treated with surgery, and after the operation there were no problems with steroid replacement or intensive insulin therapy. Of note, however: the prognosis of adrenal cancer is very poor, and the 5-year survival rate in subjects with adrenal cancer at stage III, as observed in this subject, is approximately 50% (8). Therefore, physicians should be alert for the potential recurrence of adrenal cancer.

Our subject had Werner syndrome, Cushing syndrome and adrenal cortex cancer, all of which are known to induce insulin resistance. Visceral fat accumulation and subsequent insulin resistance are characteristics of subjects with Werner syndrome (11). In addition, central obesity and consequent

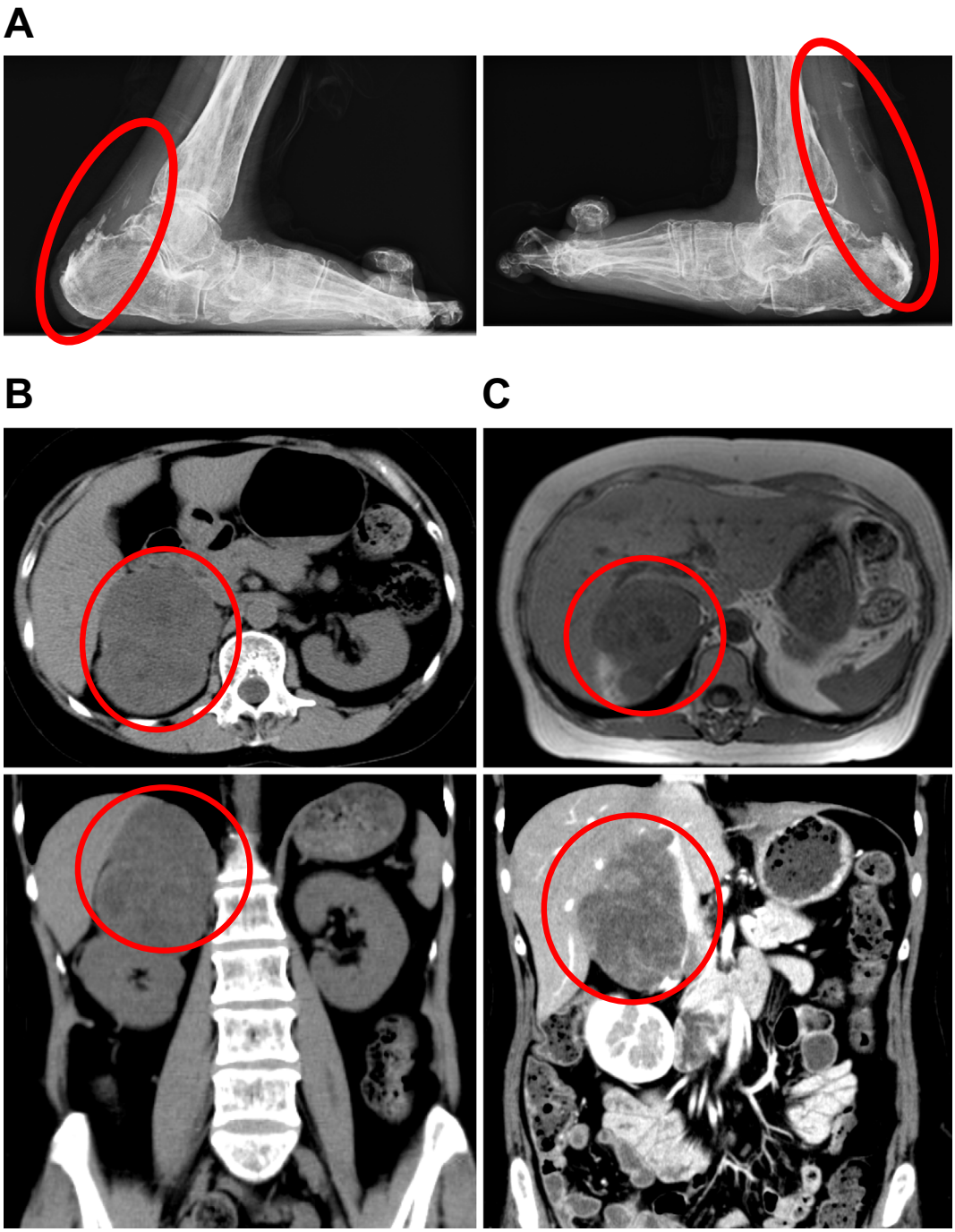

Figure 1. **(A) Significant and segmented calcification in the Achilles tendon on X-ray. (B) Neoplastic lesion in the adrenal gland on CT. The maximum diameter was approximately 8 cm, and the inside showed a mosaic pattern, including a substantial ratio of low-density area. (C) Neoplastic lesion in the adrenal gland on MRI. The maximum diameter was approximately 8 cm, and it had a high-density area due to calcification.**

insulin resistance are well-known characteristics of subjects with Cushing syndrome. Furthermore, various inflammatory cytokines, such as tumor necrosis factor (TNF)-α, are known to be secreted in subjects with malignancy, leading to the development of insulin resistance. However, in the present subject, neither central obesity nor visceral fat accumulation were observed on abdominal CT. In addition, relatively small dosages of insulin were sufficient to achieve good glycemic control. These data suggest that insulin sensitivity was relatively well preserved in this subject. We believe that, in this respect, the present subject did not show typical characteristics of Werner syndrome, Cushing syndrome or adrenal cortex cancer.

However, our subject did have several typical symptoms of Werner syndrome, such as thin, pale brown hair; a bird-like face and a harmonic and hoarse voice. In contrast, there were no typical Cushing's symptoms, such moon face, buffalo hump or red skin striae. Therefore, we assume that the

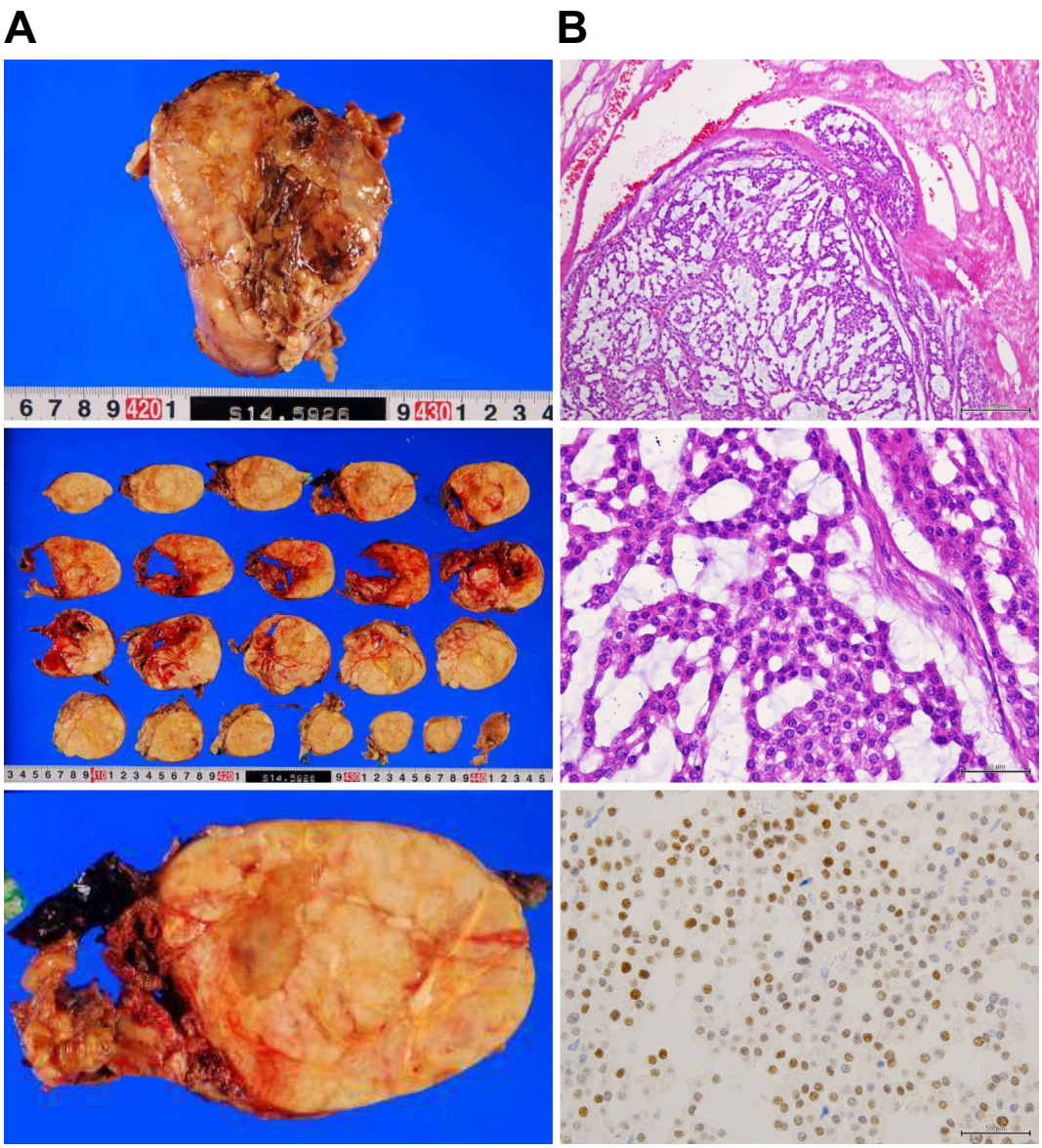

Figure 2. **(A) (Upper panel) The maximum diameter of the resected specimen was 10.5 cm. (Middle and lower panel) The cut surface was solid and myxomatous. (B) (Upper and middle panel) Dysplastic epithelium cells on Hematoxylin and Eosin staining, indicating myxoid adrenocortical carcinoma. The nuclei were relatively small, and most of the cytoplasm was eosinophilic. Necrosis and capsular invasion were observed, although no abnormal mitoses were observed. Thus, the modified Weiss' score was 4, prompting a diagnosis of adrenal cortex cancer. (Lower panel) Positive staining (brown) was observed on immunostaining for SF-1, a marker of adrenal cortex tumor.**

typical symptoms of Cushing's syndrome might have been masked by the presence of Werner syndrome, although the typical symptoms of Werner syndrome were not masked by the presence of Cushing's syndrome.

Werner syndrome and diabetes were diagnosed in the present case approximately 15 years prior to her presentation, and Cushing's syndrome was diagnosed at admission. However, since this subject did not have any typical Cushing's syndrome symptoms, and given that Werner syndrome is not usually accompanied by adrenal abnormalities, the adrenal function in this subject had not been examined until admission. Therefore, we cannot exclude the possibility that this subject had had Cushing's syndrome for a long period and that diabetes was induced by the presence of Cushing's syndrome.

There is a limitation associated with this case report. Although we understood the importance of a genetic diagnosis for achieving a definitive diagnosis of Werner syndrome and explained this point to this subject, she was extremely hesitant to undergo a genetic examination, and we failed to obtain agreement for a genetic examination from this subject. However, this subject had all of the main characteristics of Werner syndrome, including thin, pale brown hair; cataracts in both eyes; a refractory ulcer in the Achilles tendon; significant and segmented calcification in the Achilles tendon; a bird-like face and a harmonic and hoarse voice. Therefore,

we believe that we can definitively diagnose this subject with Werner syndrome based on the diagnostic criteria (12).

An epidemiological survey noted that 1,500 patients with Werner syndrome have been reported so far, 1,100 of whom were reported in Japan (13). Various types of malignancy, especially non-epithelial tumors, often accompany Werner syndrome and are a determining factor for the prognosis, in addition to coronary artery disease. Regarding the reported epithelial tumors, the frequency of thyroid cancer is relatively high. However, there has only been one report of Werner syndrome with adrenal cancer (14). The patient was a 50-year-old woman. She was diagnosed with Werner syndrome based on the presence of several progeroid manifestations and a genetic diagnosis. Her serum cortisol level was elevated, and her serum ACTH level was suppressed, points that were similar to the present case report. CT revealed a 12×10×10 cm mass in the right adrenal gland, and the adrenal tumor was diagnosed as cortical adenocarcinoma. The size and diagnosis were also similar to the subject in the present case report. In the reported case, a right ureteral tumor was noted in addition to the adrenal tumor (14). Although both tumors were resected, she developed local recurrence of the right adrenal carcinoma and multiple metastases to the liver one month after the surgery and died five months after the diagnosis. As observed in the reported case (14), double cancer is often observed in subjects with Werner syndrome, including the concurrence of epithelial and non-epithelial tumors. Therefore, we believe that we should be alert for the possibility of recurrence of adrenal cancer or the onset of other types of cancer in the present subject as well.

From the viewpoint of tumorigenesis in this subject, we hypothesized a mechanism as follows: First, the genetic cause of Werner syndrome is *WRN* gene mutations. The *WRN* gene, located on chromosome 8p, encodes a 162-kD protein of human RecQ helicase (15). RecQ helicase has multiple functions in genome maintenance, including DNA repair, recombination, replication and transcription (16). Causative mutations in the *WRN* gene induce shortening of the telomere length, which leads to chromosomal instability and a short life span of cells. We believe that such a mechanism led to the development of cancer in this subject. Second, this subject had adrenal cortex cancer, which is a very rare malignancy. It is known that the dysfunction of telomeres activates the TP53 gene, and the resultant p53 suppresses cell growth (17). In this respect, it seems that subjects with Werner syndrome are protected from the tumorigenesis caused by p53-associated processes. However, we believe that the adrenal cortex cancer in this subject may have been induced by some additional gene mutation, especially in the p53 gene, as some adrenal cortex cancers are known to be very closely associated with p53 mutations. For example, Li-Fraumeni syndrome is a rare autosomal dominant disorder characterized by familial clustering of multiple malignancies, including adrenal cortex cancer. The genetic basis of this syndrome has been defined as a germ-line mutation in the p53 gene (18). Therefore, although speculative, we think that some additional mutation of the p53 gene in the tissue of the adrenal cortex may have led to the development of the rare malignancy in this subject. Of note, however: since we did not obtain the agreement for a genetic examination from this subject, we failed to examine the mutation of the p53 gene, and therefore we cannot exclude the possibility that Werner syndrome and adrenal cortex cancer were simply coincident in this subject.

Adrenal cancer is a rare epithelial tumor. It was reported that the incident rate of adrenal cancer was 0.7-2.0 cases/year/1,000,000 subjects (6, 7). Although the subject in this case report had excess secretion of cortisol, but not androgen, many cases with adrenal cancer secrete several kinds of adrenal hormones, such as androgen, in addition to cortisol. Therefore, physicians should be careful regarding this point when caring for subjects with adrenal cancer.

Subjects with Werner syndrome are reported to have several kinds of endocrinological abnormalities, including an abnormal thyroid function, decreased gonadotropin level and decreased growth hormone response after insulin or arginine stimulation (19). However, the adrenal function is usually within the normal range in subjects with Werner syndrome. We think that the adrenal abnormality noted in this subject was due to the presence of adrenal cancer, since adrenal cancer usually secretes several kinds of adrenal hormones, such as cortisol and androgen. Indeed, adrenal abnormalities were noted in another case report of a subject with Werner syndrome and adrenal cancer (13).

Since the prognosis of adrenal cancer is known to be very poor, we should be aware of the possibility that adrenal cancer can occur in subjects with Werner syndrome and diabetes mellitus.

The authors state that they have no Conflict of Interest (COI).

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