部に 90%狭窄、左回旋枝（#12）に 50%狭窄を認め、右冠動脈狭窄部位に PCI が施行された（図 2）。

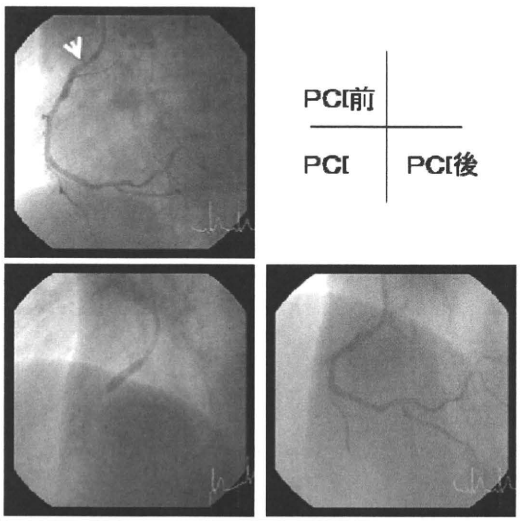

図 2　冠動脈造影
右冠動脈入口部に 90%狭窄を認め、PCI が施行された。

頭部 MRI ではラクナ梗塞を認めた（図 3）

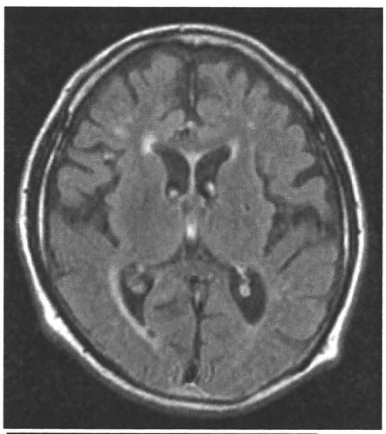

図 3 MRI FLAIR 画像

尚、本症例は経過中に肺がんを指摘され、ステージ IB (T2N0M0)との診断で左上葉切除術が施行された。その後、2009 年に咽頭がんにて 57 歳で他界された。

D．考察

平成 18 年の日本人の死亡率は悪性新生物 30.4%、心疾患 15.9%、脳血管疾患 11.8 と報告されている（厚生労働省　平成 18 年　人口動態統計月報年計）。日本人の糖尿病患者における死因は悪性新生物（34.1）、血管障害（26.8%）、感染症（14.3%）と報告されている。WS においても悪性新生物と動脈硬化性疾患は 2 大死因となっており、死因に関しては平均的な日本人や糖尿病患者と同様である。しかしながら今回の調査による動脈硬化性疾患の内訳をみると、閉塞性動脈硬化症> 冠動脈疾患≫脳血管障害の順となっていた。千葉大症例ではラクナ梗塞が認められたが、脳血管障害に関しては、平均的な日本人ならびに糖尿病患者に比較すると罹患率が低い可能性が示唆された。WS は認知症や中枢神経障害をきたしにくいことも知られている。WS に脳血管障害が少ない理由は定かではないが、RecQ 型 DNA ヘリケースの組織、細胞分布の偏りによることが原因の一つとして推測されるも、今後の検討を要する。

今回の調査では WS においては閉塞性動脈硬化症の罹患率が高いことが示されたが、WS において高率に合併する四肢末端の皮膚潰瘍と閉塞性動脈硬化に伴う下肢末梢循環不全による潰瘍形成との鑑別が困難な例が含まれている可能性があり、過大評価されていることは否定できず、さらなる詳細な調査が必要と思われた。

WS における動脈硬化性病変の形成には糖尿病や脂質代謝異常といったメタボリックな因子が深く関与していることが示唆されている。このことは糖尿病治療薬である PPARγアゴニストであるピオグリタゾンやメトフォルミンや脂質改善薬

であるスタチンがWSの寿命延長に貢献している可能性が報告されていることよりも推察される[4]。さらにRecQ型ヘリケースの変異による血管構成細胞の細胞老化も動脈硬化性病変の易形成性に関与することが示唆される。RecQ型ヘリケースはDNAヘリケースやエクソヌクレアーゼとしての機能に加えて、replication protein Aやp53といった様々なタンパクとも結合しDNAの複製、修復、細胞増殖等に関与することが知られている[5]。さらにテロメアの安定性や修復にも関与することが報告されており、このWSに認められるテロメアの異常によってゲノムの不安定性がもたらされることも報告されている[6; 7]。また酸化ストレスやテロメアの短縮によってもたらされる細胞老化をp38 MAPキナーゼの抑制することによりWS細胞の寿命や成長を改善することが報告されており[8]、治療応用といった観点では興味深い知見である。WSでは免疫系や凝固系にも異常をきたすことが報告されており[9; 10]このような要因によっても動脈硬化病変の形成が促進されることが示唆される。

E．結論

現在のWS患者における動脈硬化病変の特徴が今回の疫学結果より明らかとなった。WSは老化のモデルケースであり、WSにおける動脈硬化病変形成機序を探ることは、WSの生命予後の改善に寄与するのみならず、一般の高齢者の生命予後改善にもつながる可能性がある。今後のさらなる研究の発展が期待される。

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G．知的所有権の取得状況

1. 特許取得

なし

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IV. 研究成果の刊行物・別刷

Geriatrics Gerontology INTERNATIONAL 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2010; **10:** *319–323*

CASE REPORT

Primary lung cancer associated with Werner syndrome

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A 52-year-old man with Werner Syndrome (WS) was admitted to our hospital for the treatment of skin ulcers on his thighs. Routine chest radiography revealed an abnormal shadow in the left upper lung field. Computed tomography (CT) revealed a poorly demarcated homogeneous mass (diameter, 4 cm) in the S1 + 2 lung area; no pleural effusion was observed. CT-guided percutaneous needle biopsy revealed the presence of an adenocarcinoma. Other imaging studies did not reveal any lymph-node involvement or presence of metastatic lesions. The patient was diagnosed with stage IB adenocarcinoma (T2N0M0), and a left upper lobectomy was successfully carried out; postoperative wound healing was steady and uneventful, with no obvious ulcer formation. Primary lung cancers very rarely develop in patients with WS; non-epithelial tumors are usually observed in such patients. Patients with WS usually develop severe skin problems, such as refractory skin ulcers in the extremities; however, our patient did not develop any skin-related complications after surgery. As the expected lifespan of patients with WS is increasing, we need to pay attention not only to the rare non-epithelial malignancy, but also cancer. Further, the expected short lifespan of patients with WS, as well as the possibility of skin-related problems after surgery, should not be considered while deciding whether to take the option of surgery in the case of malignancy. **Geriatr Gerontol Int 2010; 10: 319–323.**

Keywords: adenocarcinoma, progeria, skin ulcer, Werner syndrome, wound healing.

Introduction

Werner syndrome (WS), which is also called adult progeria, is an autosomal recessive disorder caused by a mutation in the gene encoding the WS protein (WRN), which is a deoxyribonucleic acid (DNA) helicase.[1] Most of the reported cases of WS are from Japan (845 of the 1200 cases that have been reported worldwide).[2] This disease is characterized by early aging phenotypes, including graying and loss of hair, juvenile cataracts, skin ulcers, insulin-resistant diabetes and neoplasms.[3,4] The major causes of death in patients with WS are malignant tumors and atherosclerotic vascular diseases, such as coronary heart disease and cerebral vascular diseases. The ratio of incidence of malignant epithelial to malignant non-epithelial tumors in patients with WS is approximately 1:1 instead of the 10:1 ratio observed in the general population.[4] In total, 8% of patients with WS develop malignant tumors, which are usually diagnosed in the second or third decade of life. In this case, primary lung cancer was incidentally identified in a 52-year-old patient with WS; it was successfully treated with surgery, without any complications.

Accepted for publication 25 May 2010.

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Case report

A 52-year-old Japanese man was admitted to Chiba University Hospital, Chiba, Japan, for the treatment of skin ulcers on both thighs. He had been diagnosed with WS at the age of 33 years, when he had developed

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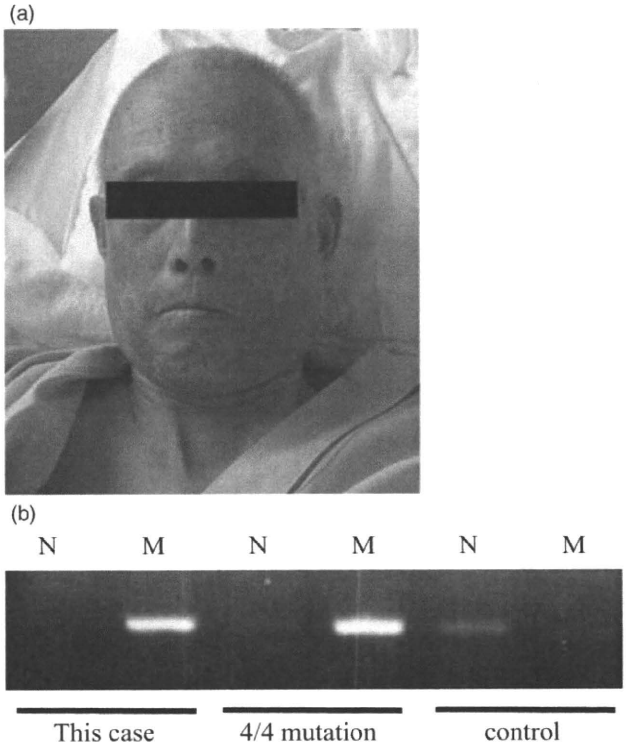

Figure 1 (a) Patient's "bird-like face", a characteristic of Werner syndrome. (b) Mutant allele-specific amplification (MASA). MASA analysis showed that the patient had the 4/4 mutation in the WRN helicase gene. M, mutation; N, normal.

bilateral cataracts. All three of his siblings had also been diagnosed with WS; however, no parental consanguinity had been reported. He had developed premature graying at the age of 15 years and was diagnosed with insulin-resistant diabetes and dyslipidemia at the age of 35 years. Since the age of 48 years, he had been treated with 10 mg of atrovastatin and 15 mg of pioglitazone. He had smoked 20 cigarettes/day from 20 to 40 years-of-age. Both his lower legs were amputated at the age of 51 years, because of intractable skin ulcers and osteomyelitis. On physical examination, we observed that he had facial features characteristic of WS; that is, he had a "bird-like" face (Fig. 1a). His voice was high pitched and hoarse; this is also a characteristic feature of WS. Multiple ulcerations, and cutaneous and subcutaneous atrophy were observed in the skin.

The complete blood cell count showed mild anemia. The results of blood biochemistry were unremarkable, except for the slightly elevated fasting blood glucose level, elevated triglyceride level and decreased high-density lipoprotein cholesterol level. To confirm the diagnosis of WS, we carried out mutation analysis based on the mutant allele-specific amplification (MASA) method.[2] The DNA from the peripheral blood leukocytes showed marked amplification for the genomic sequence corresponding to mutation 4/4 in WRN helicase, whereas this amplification was not seen in the case of control DNA (Fig. 1b); thus, the diagnosis of WS was confirmed by genetic analysis.

The patient underwent routine chest radiography on admission, which showed an abnormal shadow in the left upper lung field (Fig. 2a). CT of the lung revealed a homogeneous and poorly demarcated mass (diameter, 4 cm) in the S1 + 2 lung area; no calcification was observed (Fig. 2b). Although a portion of the pleura was invaded by the tumor, no pleural effusion was detected. The hilar, mediastinal and axillary lymph nodes were not enlarged. The levels of tumor markers for lung cancer including CEA, pro GRP, SLX and CYFRA were all within the normal range. CT-guided needle biopsy revealed the presence of an adenocarcinoma.

Magnetic resonance imaging (MRI) of the head, and CT scan and ultrasonography of the abdomen did not show any metastatic lesions. Bone scintigraphy only showed old rib fractures. The left upper lung lesion was histopathologically diagnosed as pulmonary adenocarcinoma and clinically staged as stage 1B (cT2N0M0). After providing informed consent, the patient underwent left upper lobectomy with mediastinal lymph node dissection. During the surgery, pleural indentation without pleural effusion was observed (Fig. 2c). The procedure was successful, and there were no complications.

The resected left upper lobe of the lung contained a subpleural tumor (2.8 × 2.4 × 2.2 cm), which contained solid white nodules. Although the tumor had extensively invaded the adjacent pleurae, the invasion did not extend beyond the pleurae. In addition, no metastatic lesions were observed in the lymph nodes or other lung tissue; therefore, the surgical staging of the cancer was the same as that determined before the surgery – stage IB (sT2N0M0). Histopathological examination revealed mixed cellular patterns; that is, both papillary and solid (Fig. 2d). These findings correspond to those of adenocarcinoma mixed subtype, with lymphocytic and plasma cell infiltration. No pleural invasion was observed. Pathological staging was stage IA (pT1, pN0, pm, n0, p0, br-).

Postoperative wound healing was steady and uneventful, with no obvious ulcer formation or infection. The patient was discharged on the 90th hospital day.

Discussion

Here, we report the case of a patient with WS who developed primary lung cancer that was successfully resected. WS patients usually die in the fourth decade of life, because of premature atherosclerosis and/or malignant neoplasms.[5] Strangely, in patients with WS, the incidence of malignancies of mesenchymal origin (sarcoma) was higher than that of the cancer.[3] The mechanism underlying the development of neoplasms in patients with WS remains unclear. However, several

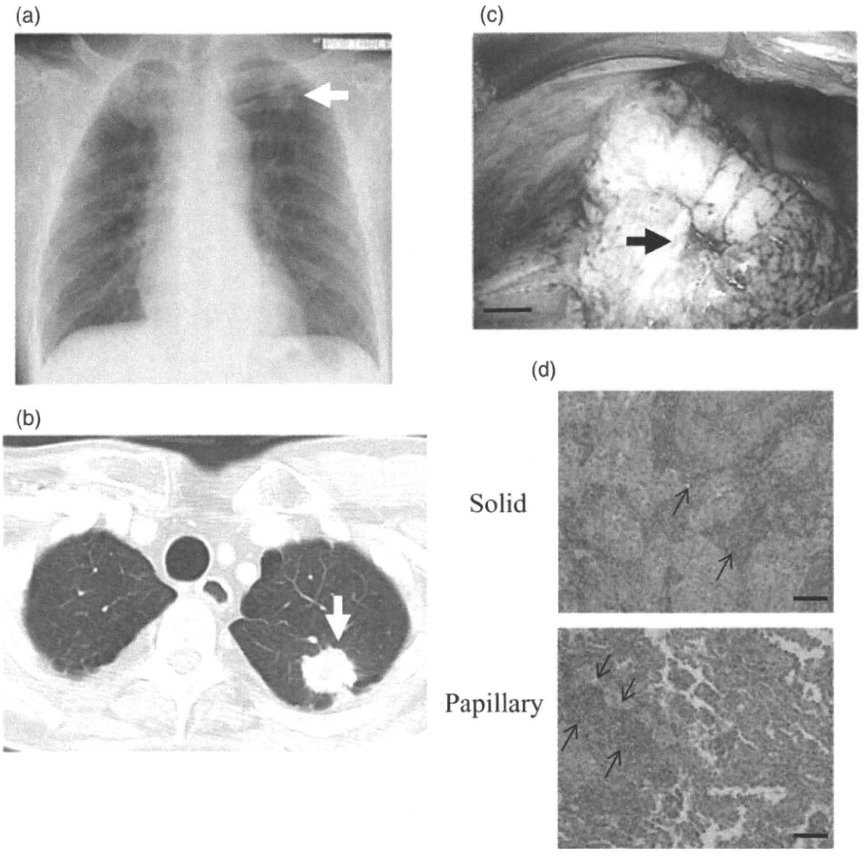

Figure 2 (a) Chest X-ray film showed an abnormal shadow in the left upper lung field, which is indicated by an arrow. (b) Computed tomography scan showed a homogenous solid tumor in the left upper lung, which is indicated by an arrow. (c). Pleural indentation without pleural effusion was observed during the surgery. Bar, 2 cm. (d) Histological specimen obtained during surgery revealed a adenocarcinoma mixed subtype; the cellular patterns were papillary and solid, with lymphocytic and plasma cell infiltration as indicated by arrows. Bar, 200 μm.

findings suggest that the WRN helicase plays an essential role in telomeric function.[6–9] The data from WRN-knockout mice indicate that the shortening and functional disability of telomeres lead to the development of osteosarcomas and soft tissue neoplasms.[10]

Lung cancer has been very rarely observed in patients with WS, probably because patients with WS have a shorter lifespan. Lung cancer develops most frequently in men who are 50 years-of-age or more.[11] Just five cases of lung cancer associated with WS have been reported so far, and all the patients were over 50 years-of-age (Table 1).[12–16]

Indeed, the recent data have shown that the lifespan of Japanese patients with WS has been significantly prolonged by approximately 10 years.[17,18] In our previous study and those of other researchers, it was reported that not only the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor (statins) therapy, but also a peroxisome proliferator-activated receptor-gamma agonist administration improves the prognosis of patients with WS.[19,20] Although the mechanism underlying this action is yet to be determined, statins might protect patients with WS as a result of the shortening of telomeres; thus, statins can extend the lifespan of patients with WS, not only by their antiatherosclerotic properties, but also by preventing the development of sarcomas. In this scenario, as the life expectancy of patients with WS increases, the incidence of cancer might also increase in the near future.

Regarding lung cancer, it is still unclear whether or not adenocarcinoma develops more often in WS patients compared with other pathological types of primary lung cancer. Four out of six cases (previous reports and the present case) are adenocarcinoma (including alveolar-epithelial carcinoma). There seems to be no difference in the pathological type of primary lung cancer between patients with and without WS, as half of all cases of primary lung cancer in non-WS patients are adenocarcinoma.[21] However, there are still very few reported cases of primary lung cancer in patients with WS. Therefore, more experience of primary lung cancer in WS patients is needed before definite conclusions can be drawn

WS patients characteristically develop skin ulcers in the extremities.[5] These ulcers are refractory to any conservative treatment and often require amputation of the limbs; this severely affects the quality of life of these patients.[22–24] The reduced proliferative capacity of the skin fibroblasts in patients with WS is likely to cause ulcer formation;[24] however, the molecular mechanism underlying ulcer formation has not yet been completely elucidated.

Table 1 Reported cases of lung cancer in patients with Werner syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5	Present case
Age, sex	54, female	51, female	52, male	52, female	55, male	52, male
Consanguinity	None	None	First cousins	First cousins	First cousins	None
Other neoplasms	None	None	None	Osteosarcoma	None	Pharyngeal cancer
Histology	Squamous cell carcinoma	Well-differenciated adenocarcinoma	Well-differenciated	Bronchio-alveolar	Squamous cell carcinoma	Well-differenciated adenocarcinoma
Stage (TNM)	1b (T2N1M0)	1b (T2NXM0)	1a (T1NXM0)	1a (T1N0M0)	1a (T1N0M0)	1a (pT1N0m0)
Treatment	Irradiation	Local chemotherapy	Left lower lobectomy	Right upper lobectomy	Left lower lobectomy	Left upper lobectomy
Outcome	14 months, died	4 months, died	Unknown	44 months, survived	47 month, survived	24 months, died
Reference	8	9	10	11	12	

Postoperative wound healing is one of the major issues considered by surgeons before deciding on surgical management in the case of patients with WS. In our patient, despite the patient's present condition and the history of refractory skin ulcers in the extremities, the lung cancer was successfully resected, without any skin-related problems. The skin and soft tissue of the extremities tend to be atrophic and comified in WS, whereas the skin of the trunk is normal.[25] In addition, subcutaneous fat tissue in the extremities of WS patients was reported to be lipoatrophic, whereas tissue of the trunk was normal. Moreover, there are possible systemic metabolic effects of regional adiposity in a patient with WS.[26] It has also been reported that not only lung cancer, but also meningiomas[27] and pancreatic cancer[28] can be successfully operated on without any skin-related problems. Therefore, there might be no difference in the wound-healing ability of the skin of the trunk between patients with WS and the normal population of the same age group. It appears that skin ulceration might not be a potential problem of surgical treatment of the trunk, as in our case and previous reports.

In summary, we report a case of WS associated with primary lung cancer that was successfully resected. As the life expectancy of patients with WS is increasing, we need to pay attention not only to rare non-epithelial malignancies, but also to epithelial cancer. Furthermore, the shorter life expectancy of patients with WS than the general population, as well as the possibility of skin-related problems after surgery, should not be a deciding factor when considering whether to carry out surgery in the case of malignancy.

Acknowledgments

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今日の診断指針 第6版

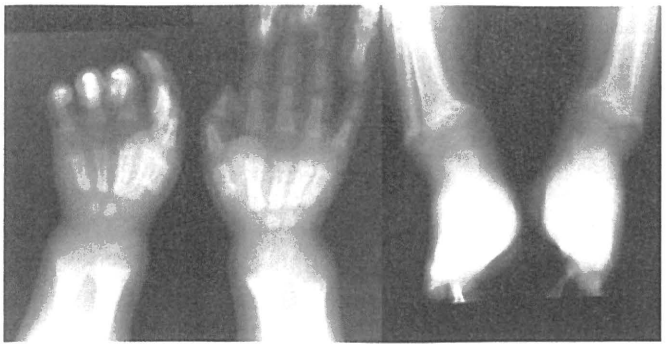

図2 くる病のX線所見

体重減少，尿意頻繁，嘔吐，不機嫌，さらに腎臓や動脈にカルシウムが沈着して異常石灰化を起こして死亡することもある。

11ビタミンE欠乏症：歩行障害，腱反射，振動感覚消失，眼球運動麻痺，網膜症を発現する。フリーラジカル捕捉障害と考えられる溶血性貧血，乳児皮膚硬化症および血小板凝集能の異常などもある。

12ビタミンK欠乏症：肝疾患やクマリン誘導体療法，胆道閉塞，腸管疾患による吸収不全により起こり，出血傾向を示す。

検査とその所見の読みかた(表1)

1ビタミンB_1欠乏症では，血中ビタミンB_1濃度の低下，赤血球トランスケトラーゼ活性の低下，血中ピルビン酸および乳酸値の増加がみられる。

2ビタミンB_{12}欠乏症では，血中ビタミンB_{12}濃度低下，LDH増加，尿中メチルマロン酸排泄量増加，巨赤芽球の出現，白血球および血小板の形成障害がみられる。

3血中25-水酸化ビタミンD(25-OHD)濃度は15～40 ng/mLで，ビタミンDの栄養状態を示す。ビタミンD欠乏では血中カルシウムやリン濃度は低下し，副甲状腺ホルモン(PTH)やアルカリホスファターゼ活性は上昇する。

4ビタミンK欠乏では，異常プロトロンビンであるPIVKA-Ⅱ(proteins induced by vitamin K absence or antagonist)が血液中に増加する。

治療法ワンポイント・メモ(表1)

1イソニアジド，ペニシラミン，サイクロセリンはビタミンB_6拮抗剤が含まれているので，使用時はビタミンB_6を1日に30～100 mg投与によって予防する。

2ビタミン剤の補給により症状だけでなく，予備能まで回復させる。

3発症の原因を解決しておく。

4生活習慣を改めるなどである。

さらに知っておくと役立つこと

1成長・妊娠・授乳・発熱などによる必要量の増大

2飢餓，アルコール常用者や菜食主義など食品摂取の偏りや摂取量の不足

3新生児の腸管，抗菌薬投与や下痢による腸内細菌叢の変化

4肝臓や腎臓障害によるビタミンの活性化障害

5胃腸障害，胆嚢・肝臓・膵臓障害，胃腸切除などによる吸収障害などである。

Werner症候群**

Werner Syndrome

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診断のポイント

1若年性両側性白内障。30歳代までに指摘されることが多い。

2四肢末梢，特に足部の角化性皮膚変化。胼胝・鶏眼が好発。難治性潰瘍を生じやすい。

3毛髪変化。白毛や脱毛を認める。

4高調性の嗄声。

5軟部組織(特にアキレス腱)の石灰化。

症候の診かた

20歳前後より上述の諸症状がみられるようになる。このほか，低身長，鳥様顔貌(鼻や口先が尖って見え，鳥の嘴を連想させる)，体幹に比べ四肢が著しく細い，などの特徴がある。全身像を図1に示す。

検査とその所見の読みかた

1臨床所見から本症を疑った場合，アキレス腱のX線撮影で踵骨付着部近傍に石灰化を認めれば，ほぼ本症と診断できる(図2)。

2高インスリン血症を伴う糖尿病や脂質異常症を50%以上の症例で認める。

3四肢末梢の骨密度低下を示しやすい。

確定診断のポイント

原因となるWRN DNAヘリケースの変異を確認

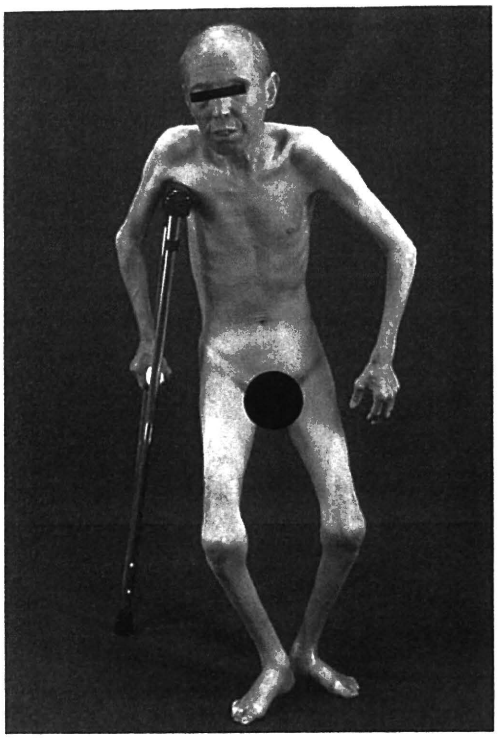

図1 全身像
(51 歳男性)

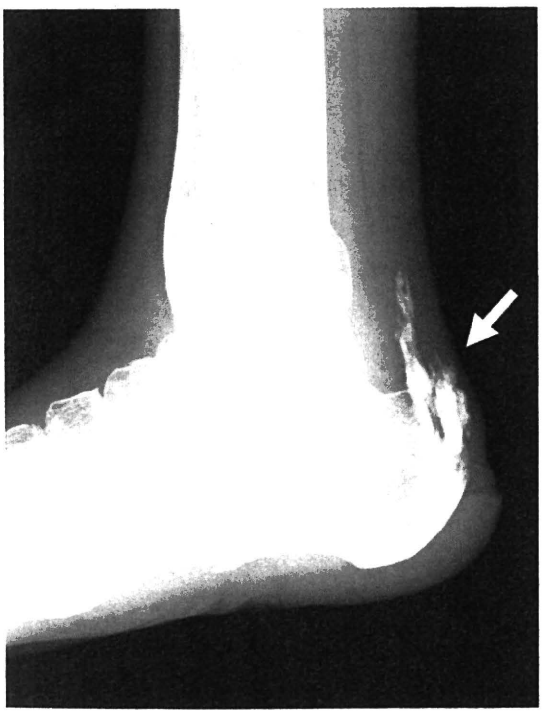

図2 アキレス腱石灰化像(右踵部側面 X 線撮影，50 歳女性)
石灰化部位を矢印で示す。

表1 Werner 症候群の診断基準

Ⅰ 主要徴候(10 歳以上での発症)
1. 白内障(両側性)
2. 特徴的な皮膚変化(硬化，萎縮，色素沈着，潰瘍，角化，部分的な皮下組織の萎縮)と顔貌(鳥様顔貌)
3. 低身長
4. 両親の近親婚または兄弟の罹患
5. 白髪や脱毛の早期出現
6. 24 時間尿中ヒアルロン酸試験陽性(実施可能な場合)

Ⅱ そのほかの徴候
1. 糖尿病
2. 性腺機能低下(二次性徴未発達，不妊，精巣や卵巣の萎縮)
3. 骨粗鬆症
4. 手指・足趾末節骨の硬化(X 線診断)
5. 軟部組織の石灰化
6. 早発性動脈硬化(例：心筋梗塞の既往)
7. 間葉系新生物，希少なまたは多発性の新生物
8. 音声変化(高調のきいきいした嗄声)
9. 24 時間尿中ヒアルロン酸試験陽性(実施可能な場合)
10. 扁平足

Ⅲ 判定
確実例：Ⅰのすべてと Ⅱの 2 つ以上
疑い例：Ⅰの 1，2，3 とそれ以外の徴候 2 つ以上
可能性あり：白内障または皮膚変化のいずれかとそれ以外の徴候 2 つ以上
否定的：思春期以前の症状出現(ただし，身長を除く)

〔Werner 症候群国際登録組織(International Registry of Werner syndrome)，http://www.wernersyndrome.org/registry/diagnostic.html より引用・和訳・一部改変〕

鑑別すべき疾患と鑑別のポイント

全身硬化症(強皮症)(⇨ 1550 頁)。毛髪変化や白内障の存在などから鑑別が可能。国際的に提唱されている診断基準の一つを表 1 に示す。

予後判定の基準

悪性腫瘍と冠動脈疾患の合併が生命予後に影響する。一方，潰瘍を代表とする足部の皮膚病変は疼痛のほか感染を伴いやすく，車いす生活への移行や下肢切断など，患者の生活予後/QOL を左右する。

合併症・続発症の診断

1 悪性黒色腫，骨肉腫，骨髄異形成症候群，髄膜腫などの間葉系腫瘍，そして甲状腺癌の合併が多く，膀胱癌や肺癌もみられる。早期発見により根治も可能である。

2 内臓脂肪蓄積，耐糖能障害，脂質異常症など，メ

する。末梢血を用いた遺伝子・蛋白の検査を，千葉大学およびジーンケア研究所(神奈川)において実施可能である。

タボリックシンドロームに似た病態を呈し，その結果として動脈硬化性疾患を生じやすい。

治療法ワンポント・メモ

1 合併する糖尿病には，通常，チアゾリジン誘導体が著効を示す。

2 冠動脈疾患のハイリスク群と考え，脂質，血糖，血圧の適切な管理を行う。高 LDL コレステロール血症にはスタチンが有効である。

手術適応のポイント

1 足部や肘部の難治性皮膚潰瘍に対して，しばしば皮膚移植が奏効する。

2 四肢末梢と異なり，体幹部の皮膚は柔軟性や再生能が保たれているため，通常，胸腹部の手術実施には支障がない。

さらに知っておくと役立つこと

1 平均寿命は，従来 40 歳代といわれてきたが，近年 50 歳代半ばへと延長し，60 歳を超える患者も存在する。生命予後を左右する悪性腫瘍の早期発見と治療，冠動脈疾患を予防するためのリスク管理，足部潰瘍の適切な処置が予後改善に重要である。

2 40 歳頃より性腺機能低下を認めるが，通常，20〜30 歳代には生殖可能である。

3 "早老症"と呼ばれるものの，全身があまねく老化徴候を示すわけではなく，例えば認知症の合併は多くない。

4 日本における有病率は 5〜10 万人に 1 人。常染色体劣性遺伝形式をとる。

〔執筆協力：本城 聡　千葉大学大学院・細胞治療学〕

V. 参考資料