



REVIEW / *Musculoskeletal imaging*

Radiographic presentation of musculoskeletal involvement in Werner syndrome (adult progeria)



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KEYWORDS

Werner syndrome;
Musculoskeletal system;
Soft-tissue calcification;
Adult progeria;
X-ray

Abstract Werner syndrome (i.e., adult progeria) is a rare autosomal recessive disorder caused by mutations of the *WRN* gene, which is characterized by the premature appearance of features associated with normal aging and cancer predisposition. Patients with Werner syndrome can present with musculoskeletal complaints, associated with suggestive radiographic features with a potential prognostic or therapeutic impact. This review illustrates the main radiographic features of Werner syndrome, focusing on the musculoskeletal system, such as soft-tissue calcification, muscular atrophy, osteoporosis, foot deformities, osteitis and osteomyelitis, and bone or soft-tissues malignancies. The identification of these features by radiologists can therefore be useful in the clinical screening of Werner syndrome.

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Werner syndrome (also known as adult progeria) was originally described as scleroderma-like thinning and stiffening of the skin with bilateral cataracts [1]. This rare condition is an autosomal recessive disorder caused by mutations in the *WRN* gene, a member of the RecQ DNA helicase family [2], which is involved in the surveillance of newly synthesized daughter-strands of DNA for incorporation errors, and their repair [3]. WS manifests as an

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accelerated form of the human aging process. Symptoms usually begin during the second decade of life. Patients with WS can present with musculoskeletal complaints, associated with suggestive radiographic features with a potential prognostic or therapeutic impact.

The purpose of this review was to describe the radiographic features of musculoskeletal involvement in WS. It is assumed that familiarity with these features by radiologists can therefore be useful in the clinical screening of patients with WS.

Clinical background

The diagnosis of WS is usually made many years after the initial presentation. A much higher incidence of WS is encountered in the Japanese population [4]. Usual clinical features include short stature, a characteristic "birdlike" facies, premature hair graying with alopecia, scleroderma-like skin changes (thin, tight, atrophic skin, pigmentary alterations, loss of subcutaneous fat, refractory skin ulcers) and musculoskeletal manifestations [2,5,6]. Bilateral cataract, abnormal glucose and lipid metabolism, and hypogonadism are also common in patients with WS [2,5]. Premature atherosclerosis and malignant tumors are the most common causes of death [7]. Molecular confirmation of the diagnosis is made by combining nucleotide sequencing by reverse transcription polymerase chain reaction with Western-Blot protein analysis [8].

The description of imaging features of musculoskeletal involvement in WS is mainly based on X-rays and computed tomography (CT). Magnetic resonance imaging (MRI) findings in patients with WS have only been reported for soft-tissue tumor, osteomyelitis and soft-tissue calcification [9,10].

Because of the similarity in skin changes between WS and systemic sclerosis, patients with WS can be misdiagnosed as having systemic sclerosis. Both subcutaneous calcification and muscular atrophy are associated with systemic sclerosis [11]. However, the other musculoskeletal abnormalities of WS are not usually encountered in systemic sclerosis. Hyperphosphatemia,

hyperparathyroidism, hypervitaminosis D, neoplasms, excessive mechanical stress and inflammatory diseases may also cause ectopic calcifications [10,12]. Inflammatory diseases associated with ectopic calcifications, especially with a periarticular location include scleroderma, dermatomyositis and systemic lupus erythematosus [13].

Some of skeletal manifestations encountered in WS have a prognostic or therapeutic impact. In this regard, the incidence of osteosarcoma and soft-tissue sarcoma is higher in patients with WS by comparison with the general population. In addition, malignant tumors are one of the most common causes of death [7]. Furthermore, some of the symptoms associated with the radiographic features may benefit from a medical treatment. Honjo et al. have reported that administration of sodium etidronate led to the improvement of painful soft-tissue calcification in patients with WS [14]. Noda et al. also suggested that bosentan (Tracleer[®], Actelion Pharmaceuticals), which is a dual endothelin receptor antagonist, could be a promising treatment option for intractable cutaneous ulcers in WS [15]. Walton et al. reported number of complications after surgical procedures in patients with WS, probably due to the lack of bone healing and soft-tissue repair in these patients [9]. They suggest that feet deformities may be best managed with orthotics [9].

Musculoskeletal manifestations

Soft-tissue calcification

Soft-tissue calcification, especially in the Achilles tendon, is one of the most common manifestations of WS [2]. Ectopic soft-tissue calcification was originally identified in 33% (40/120) of patients with WS [2]. However, the actual incidence of soft-tissue calcification in WS may be higher [7]. In this regard, a study involving 72 patients with WS radiographs showed calcification of the Achilles tendon in 80% of them [5]. Ectopic calcification is often associated with dermal symptoms [7]. The identification of the soft-tissue calcification by X-rays, in patients complaining



Figure 1. Radiographs of a 33-year-old man with Werner syndrome: a: lateral radiograph of both knees shows linear calcification of the patellar tendon and the quadriceps tendons (arrows); b: lateral radiograph of the left elbow shows tendinous calcification arising from the superior aspect of the olecranon process, regarding the triceps tendon (arrowhead).



Figure 2. Radiographs of a 38-year-old man with Werner syndrome: a: lateral radiograph of the right knee shows heterotopic soft-tissue calcification of the quadriceps tendon and the patellar tendon, with a segmentar pattern (arrows); b: lateral radiograph of the left knee shows heterotopic soft-tissue calcification prominent in the patellar tendon, with a flame-like shape (arrow); c: lateral radiograph of the right foot shows soft-tissue calcification in the subcutaneous fat adjacent to Achilles tendon (arrowheads). Note also the presence of an erosion of the calcaneus related to chronic osteitis (arrow); d: radiograph of both femoropatellar joints shows erosion of right patella related to chronic osteitis (arrow). Note also the presence of soft-tissue calcification (arrowheads).



Figure 3. Radiographs of a 58-year-old woman with Werner syndrome: a: postero-anterior radiograph of both hands shows punctiform soft-tissue calcification with a periarticular location around interphalangeal joints (arrowheads); b: lateral radiograph of the left foot shows tendinous calcification in Achilles tendon and in plantar aponeurosis, with a segmental pattern (arrowheads). Note also the presence of two bone screws related to hallux valgus surgery (arrow); c: postero-anterior radiograph of both feet shows two bone screws related to prior left hallux valgus surgery (arrow).

of pain and refractory skin ulcers, may help physicians consider the diagnosis of WS, showing periarticular calcification with flame-like or segmental patterns (Figs. 1–3) [5]. In difficult cases, CT can help better localize these calcifications [10]. MRI analysis may be helpful to investigate the tendinous complications of soft-tissue calcification, such as tenosynovitis by individualizing fluid accumulation in the tendon sheath or tendon disruption presenting as an increased signal intensity of the edges of the tendon [10].

Several authors also reported extensive calcification leading to skin ulceration in WS patients [10,14,16]. These findings suggest that soft-tissue calcification is closely

associated with dermal symptoms including refractory ulcers and pain in WS patients [12].

Muscular atrophy

Marked muscular atrophy is a consistent musculoskeletal finding in WS. It most notably affects the limbs, contrasting with a relative sparing of the trunk [1,2]. This has been found in more than 90% of patients with WS [9]. Biochemical investigations, especially creatine kinase serum levels, usually demonstrate a normal muscle biochemistry while electromyography is unrevealing [2,17]. Loss of the muscular volume can be roughly evaluated on limbs radiographs.

Osteoporosis

Osteoporosis is a common radiographic manifestation in WS, encountered in 40% to 100% of patients [17,18]. Osteoporosis in WS is more severe in distal limb bones, than in the vertebral column [19], which is more affected in the general population [2,20]. Vertebral deformities (such as vertebral wedging, spondylolistheses, pathological fractures and lumbar lordosis), and insufficiency fractures of the limbs have been reported in patients with WS and osteoporosis [21,22]. Treatment with human insulin-like growth factor has been attempted in such cases of osteoporosis [23].

Foot deformities

Foot deformities have also been described in patients with WS (Fig. 3). Pes planus, hallux valgus and flexion contractures of the ankle are the most commonly reported ones, with prevalence ranging from 35% to 43% [9,17,18]. This type of deformities may be related to chronic ulcerations with subsequent infection and to neurovascular factors [9].

Osteitis and osteomyelitis

Patients with WS may present with osteomyelitis and osteitis on radiographs, described as destructive changes with lytic areas in bones (Fig. 2) [18]. MRI findings of osteomyelitis include hypointensity of the bone marrow on T1-weighted MR images, increased signal intensity on short tau inversion recovery (STIR) images, soft-tissue swelling and inflammation [10]. Such infections could be related to neurotrophic changes in the feet and chronic skin ulceration, which is a constant feature in WS [17,18].

Neoplasia

WS is characterized by a high predisposition to malignancies, with 10% of all patients with WS who develop tumors, 50% of which are soft-tissue and/or bony sarcoma [24–26]. Soft-tissue sarcomas in patients with WS include malignant schwannoma, rhabdomyosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, and other rare tumors [26]. Osteosarcoma is the malignant bone tumor associated with WS [26]. Osteosarcomas in WS patients are more commonly developed in the lower extremities, whereas they predominantly affect the upper extremities in the general population [8,26,27]. It is thus important to diagnose WS at an early stage, and to further investigate patients with clinical signs that may suggest bone or soft-tissue sarcoma.

Other abnormalities

Reduced metacarpal cortical thickness is another radiological abnormality in patients with WS [28]. Goto et al. have suggested that the radiographic combination of periarticular calcification, phalangeal osteosclerosis in the hand or foot and osteoporosis should lead to the diagnosis of WS [28].

Conclusion

WS is a rare autosomal recessive disorder characterized by a wide spectrum of clinical features associated with premature aging, including musculoskeletal manifestations. Soft-tissue calcification, muscular atrophy, osteoporosis, foot deformities, osteitis and osteomyelitis, bone and soft-tissues malignancies, and other bony abnormalities have been described. Patients with WS can occasionally visit physicians because of musculoskeletal complaints, and radiologists should be aware of the radiographic features of this rare condition.

Disclosure of interest

The authors declare that they have no competing interest.

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