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REVIEW / *Musculoskeletal imaging*

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

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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.

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

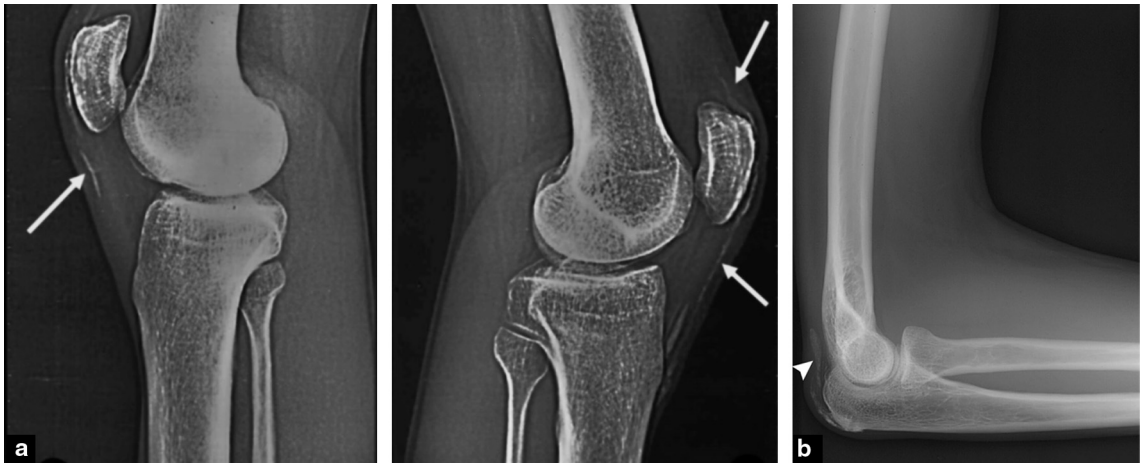

Figure 1. Radiographs of a 33-year-old man with Werner syndrome: a: lateral radiograph of both knees shows linear calcification of the patellar tendon and the quadricipital tendons (arrows); b: lateral radiograph of the left elbow shows tendinous calcification arising from the superior aspect of the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

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