Singleton-Merten syndrome: A rare cause of femoral head necrosis

Elio Assaf1 | Mohamad Bdeir1 | Elisabeth Mohs1 | Franz-Joseph Dally1 | Sascha Gravius1 | Cleo-Aron Weis2 | Ali Darwich1

1Department of Orthopedics and Trauma Surgery, University Medical Centre, Medical Faculty Mannheim of the University of Heidelberg, Mannheim, Germany
2Institute of Pathology, University Medical Centre, Medical Faculty Mannheim of the University of Heidelberg, Mannheim, Germany

Correspondence
Elio Assaf, Department of Orthopedics and Trauma Surgery, University Medical Centre, Medical Faculty Mannheim of the University of Heidelberg, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, Germany.
Email: elio.assaf@umm.de; elio.assaf@hotmail.com

Abstract
Singleton-Merten syndrome (SMS) is a type I interferonopathy. In this report, we disclose the first—to the best of our knowledge—direct association of SMS with femoral head necrosis (FHN). The following case report presents the condition of a 38-year-old male suffering from SMS with FHN, characterized by acute symptoms and rapid disease progression. As per the recommendations of the Association Research Circulation Osseous (ARCO) and the S3-guidelines, we successfully treated the FHN with core decompression. Our histological results correlate with the changes described in medical literature in patients with SMS and MDA5-knockout in vivo experiments such as osteopenia, widened medullary cavity, and thin cortical bone. Moreover, the conducted immunohistochemistry shows strong CD56 positivity of the osteoblasts and osteocytes, as well as significant CD68 and CD163 positivity of the middle-sized osteoclasts. Collectively, these findings suggest an underlying syndrome in the FHN. A six-month post-operative follow-up revealed complete recovery with the absence of the initial symptoms and ability to resume normal daily activities. Taken together, our findings suggest that SMS is an additional cause of FHN in young adults. Early detection and adequate treatment using well-established joint-preserving techniques demonstrate a favorable improvement of the patient’s clinical condition.

KEYWORDS
core decompression, femoral head necrosis, MDA5, rare disease, Singleton-Merten syndrome

1 INTRODUCTION

Singleton-Merten Syndrome (SMS) is a type I interferonopathy characterized by dental dysplasia, aortic calcification, skeletal abnormalities, glaucoma, and psoriasis. Other common clinical findings include fever of unknown origin, muscular weakness, and foot deformities. Skeletal demineralization and osteoporosis with deformation of metacarpals and phalanges shafts are also typical findings of the SMS.

According to Rutsch et al. (2015), common missense mutation, c.2465G>A (p. Arg822Gln), in the interferon-induced helicase C domain 1, IFIH1, caused SMS in five patients from three different families, including the patient described in this report. This gene encodes the melanoma differentiation-associated protein 5 (MDA5), a member of the RIG-I-like receptor (RLR) family and an integral sensor in the type I interferon pathway.

Cellular and biochemical assays by Rice et al. (2014) suggested that these mutations cause a gain of function: mutant IFIH1 binds
RNA more avidly, leading to an increase in baseline and ligand-induced interferon signaling.

Furthermore, Jang et al. (2015) reported pathogenic variants in DDX58, which encode another cytosolic double-stranded RNA sensor, a member of the RLR family. These variants are associated with a milder phenotype of SMS and consequently with a better prognosis.

However, a direct association of SMS with FHN was not previously described among phenotypes of the syndrome in the medical literature. Therefore, in the following article, we present the first reported case of SMS associated with FHN.

2 | CASE DESCRIPTION

A 38-year-old male with a confirmed diagnosis of Singleton-Merten Syndrome (SMS) presented to our outpatient clinic with increasing pain in the left groin that started several months back and became more prominent in the last 4 weeks prior to presenting to the clinic. The pain later progressed onto the left thigh without any report of weakness or history of trauma in the lower leg.

The clinical presentation at the time of the initial diagnosis and the evolution of the symptoms until the age of 30, is described in the work of Feigenbaum et al. (2013).

Bone morphology was studied via iliac bone biopsy, which showed cortical width at 68% of the mean for age and normal bone volume. Surface-based parameters of bone turnover were within normal limits, bone formation was at 87% of the mean for age, and mineralization was typical. No pathogenic mutation in ENPP1 was found. ENPP1 encodes ectonucleotide pyrophosphatase/ phosphodiesterase 1, which is responsible for the generation of inorganic pyrophosphate, a natural inhibitor of mineralization (Eytan et al., 2013; Rutsch et al., 2003). Moreover, serum levels of receptor activator of NF-kappaB and osteoprotegerin were within normal range (Van Campenhout & Golledge, 2009; Zhao et al., 2011).

The medical history of the patient included a combined heart defect (vitium aortic-mitral) with mechanical valvular replacement of both valves in 2005 and revision in 2010 after endocarditis, tendinopathy of the fingers and toes, dental dysplasia with prosthetic implants in the upper and lower jaw, a perioperative embolic event of the cerebellum in July 2005 with recurrent epilepsy crises, rupture of the Achilles tendon in 2002, rupture of the quadriceps tendon in 2004, first-degree AV block, mild left ventricular failure, iatrogenic intraoperative lesion of the left ulnar nerve in 2014 secondary to a plate osteosynthesis of the left humerus, splenomegaly secondary to a splenic infarction, and depression since 2000.

Furthermore, the patient was on anticoagulant therapy with phenprocoumon since 2005 after his valvular replacement. The remaining medications included metoprolol succinate, pantoprazole, sertraline, as well as eye drops with (R)-timolol hydrogen maleate and brimonidine (R, R)-tartrate.

3 | CLINICAL FINDINGS

At the initial presentation in our outpatient department, there were no unusual clinical findings detected in the left hip and thigh. The range of motion (ROM) of the left hip was relatively normal. The patient reported pain in the left groin and in the greater trochanter region with hip flexion above 120° and abduction above 40° respectively.

4 | DIAGNOSTIC ASSESSMENTS

The completed radiographs as shown in Figure 1 did not show any bone damage or collapse of both hip joints. We noticed grade 3 early arthritis signs on both sides, as per the Kellgren and Lawrence classification (Kohn et al., 2016).

Considering the vascular modifications occurring in the described syndrome, we suspected an emerging FHN as a cause of the patient’s discomfort. Therefore, we conducted an MRI to define the extent and nature of the suspected lesion in accordance with the S3-guidelines (Bohndorf et al., 2015). The MRI images revealed second stage FHN, based on the Association Research Circulation Osseous (ARCO) classification (Figure 2) (Bohndorf et al., 2015; Roth et al., 2016; Schmitt-Sody et al., 2008).

With reference to the S3-guidelines, we further performed a computer tomography (CT) of the pelvis. The images obtained did not display any bone damage, collapse, or signs of subchondral insufficiency fractures (Figure 3).

We thus confirmed our initial diagnosis of FHN with ARCO stage II and suggested core decompression as a well-established therapeutic modality (Roth et al., 2016).

Shortly afterward, the patient reported an acute worsening of the pain and of the maximal ROM of the left hip to a maximal flexion of 90° and a maximal abduction of 10°. Subsequently, we discussed with the patient both therapeutic modalities (conservative and surgical) and the possible surgery-associated risks. The
anticoagulation therapy could not be preoperatively stopped or bridged because of the above-described two valve-replacements as well as the SMS induced advanced vascular sclerosis and high embolism risk.

5 | THERAPEUTIC INTERVENTIONS

Because of the acute clinical exacerbation during the last 3 weeks the patient opted for the operative therapy despite the risk of a postoperative bleeding. We planned a mini open surgery using a joint-preserving technique: core decompression with biopsy of the left femoral head (Figure 4).

A deep subfascial hemorrhage of the thigh occurred 4 days postoperatively under the full anticoagulation therapy. The patient was transfused with four red cell concentrates in 4 days. The conducted CTA (Computed Tomography Angiography) revealed a large subfascial hematoma around the proximal femur without active bleeding (Figure 5). The hematoma was then surgically evacuated, and the hemostasis optimized by reducing the anticoagulation therapy and implementing an off label-use of Nadroparin-Calcium for 3 days. The patient was then discharged on the fourth postoperative day.

6 | FOLLOW UP AND OUTCOME

Physical examinations 4 weeks and 6 months after the surgical intervention revealed a wider ROM of the left hip with satisfactory remission and complete relief of the previous symptoms. The overall non-specific histological findings were compatible with the changes described in the literature in patients with SMS and in MDA5-knockout experiments including osteopenia, widened medullary cavity, and thin cortical bone (Soda et al., 2019) (Figure 6). Moreover, immunohistochemistry data showed a strong CD56 positivity of the osteoblasts and osteocytes as well as a strong CD68 and CD163 positivity of the middle-sized osteoclasts (Rutsch et al., 2015).

Finally, the correlation of the radiological findings (X-ray, CT, MRI) with the obtained final pathological examination suggests a direct relationship between the SMS and the FHN.

7 | DISCUSSION

SMS is a rare disease with very few cases reported in the literature. Common features include abnormal aortic calcification, abnormal ossification of extremities, and dental anomalies (Bursztejn et al., 2015;
Ozyuksel et al., 2014). Other associated characteristics are glaucoma, psoriasis, tendinitis, and osteoporosis (Feigenbaum et al., 2013).

While SMS is believed to cause a series of functional and physiological impairments of the skeletal system at many levels in terms of structure, length, consistency, strength, and vascularization of bone, it remained—so far—an unknown underlying cause of FHN (Kamal et al., 2018). This case report is the first report depicting the existence of a FHN association with SMS. In the present case, the therapy with joint-preserving surgical technique by means of core decompression led to a clear reduction in symptoms and an increase of the ROM of the affected hip (Bohndorf et al., 2015; Roth et al., 2016; Zhang et al., 2018). The first pathological examination revealed the well-defined changes in the femoral head as osteopenia and widened medullary cavity, that are usually atypical findings in the normal adult bone despite FHN (Kamal et al., 2018). The conducted immunohistochemistry showed a strong CD56 positivity of the osteoblasts and osteocytes as well as a strong CD68 and CD163 positivity of the middle-sized osteoclasts (Rutsch et al., 2015), compatible with the changes described in the literature in patients with SMS and in MDA5-knockout experiments (Soda et al., 2019).

Moreover, the immunohistochemistry findings revealed the localization of MDA5 in all representative tissue samples. Those results correlate with the previously defined changes in blood and dental cells among individuals affected with SMS where the IFIH1 c.2465G>A mutation enhanced MDA5 function in interferon beta induction (Pettersson et al., 2017; Rutsch et al., 2015).

Findings described by Rice et al. (Rice et al., 2020) suggest IFIH1 gain-of-function as a cause of a type I interferonopathy involving a wide spectrum of autoinflammatory phenotypes including Aicardi-Goutières syndrome and Singleton-Merten syndrome. Their data confirms variable expression and non-penetrance as important features of the IFIH1 genotype. This includes constant association with enhanced type I interferon signaling and a common mutational mechanism involving improved RNA binding affinity or even decreased efficiency of ATP hydrolysis and filament disassembly rate (Rice et al., 2020).
The anticoagulation therapy in this case could not be preoperatively stopped or bridged due to the above-mentioned two-valve replacement as well as the advanced vascular sclerosis and therefore, high risk of embolism. However, the severe form of FHN with the acute clinical exacerbation led to the operative therapy despite the risk of postoperative bleeding.

Even though core decompression is a less invasive surgical intervention associated with low perioperative complications, the patient presented major bleeding complications which led to the transfusion of four red cell concentrates over the course of 4 days. An off-label bridging of his anticoagulation as well as a second surgical intervention with evacuation of the hematoma led to a favorable outcome and a discharge of the patient in the ambulatory convalescence.

SMs describes a variety of changes that affect the skeletal system. In the case of pain in the hip joint, underlying damage to the femoral head (FHN) must be considered (Feigenbaum et al., 2013). Extended hip imaging, especially an early MRI, helps making a timely diagnosis. Depending on the clinical and image-morphological findings, a joint-preserving procedure can be discussed to improve the quality of life and to slow the progress of necrosis. A collapse of the femoral head inevitably leads to prosthetic total hip replacement (Pettersson et al., 2017).

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS
Elio Assaf: conceptualization, acquisition of data, writing—original draft; Mohamad Bdeir: acquisition of data, analysis, and interpretation of data; Elisabeth Mohs: acquisition of data, analysis, and interpretation of data; Franz-Joseph Dally: acquisition of data, analysis, and interpretation of data; Sascha Gravius: conceptualization, design, review & editing, supervision; Cleo-Aron Weis: conceptualization, analysis, and interpretation of data; Ali Darwich: conceptualization, design, review & editing, supervision; All authors read, revised, and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ORCID
Elio Assaf https://orcid.org/0000-0002-3105-0356

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