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Challenges in identifying the underlying cause of extensive osteonecrosis: an illustrative example and clinical guide

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The authors present a case of a female patient in her early forties diagnosed with an exceptionally extensive manifestation of osteonecrosis, with bilateral involvement across several major joints and bone regions, including the proximal femur, distal femur, proximal tibia, patella, and the foot/ankle area. The widespread pattern suggested a severe systemic compromise in blood flow, leading to ischemic bone damage. To elucidate the underlying pathology, a comprehensive array of tests and investigations were conducted. As the case advanced, a potential elementary cause for the osteonecrosis was identified: alcohol abuse.

INTRODUCTION

Osteonecrosis, also referred to as avascular necrosis (AVN) or ischemic bone necrosis, is a pathologic condition in which the interruption of blood supply leads to bone tissue necrosis[1]. It is estimated that between 10.000 to 20.000 adult patients are diagnosed with this condition annually in the United States[2]. A hallmark symptom is progressive pain, resulting from bone and joint deterioration occurring within months to years following the initial ischemic event[1]. This pain is typically associated with load-bearing activities[3]. In approximately two-thirds of patients, pain may also be present in the absence of movement or weight-bearing activities and one-third of patients experience pain at night[4]. Bone infarction most commonly affects a single area or joint, with the femoral head, distal femur, proximal and distal tibia, talus and humeral head being the most frequently involved sites[5]. In rare instances, multiple areas are affected simultaneously . A patient is suffering from multifocal osteonecrosis if 3 or more joints are affected[5]. The pathogenesis of osteonecrosis is believed to result from a combination of genetic predispositions, local vascular factors affecting blood supply, metabolic factors, vascular injury, mechanical stressors and increased intraosseous pressure[1].

The most prevalent causes of osteonecrosis are traumatic fractures[1,5]. Another common cause is the prolonged systemic use of glucocorticoids[6] The use of bisphosphonates or other antiresorptive agents is specifically associated with an increased risk of osteonecrosis of the mandible[7]. This risk is heightened in patients using these medications for malignant diseases, such as multiple myeloma or metastatic breast cancer[7]. Excessive alcohol consumption is another frequently observed aetiological factor, leading to vascular and metabolic changes within the bone. Nicotine abuse is also a recognized risk factor, particularly for osteonecrosis of the femoral head[8]. Underlying conditions that are known to contribute to the development of osteonecrosis are systemic lupus erythematosus (SLE), sickle cell hemoglobinopathies, Gaucher disease, heritable osteonecrosis, clotting disorders such as inherited thrombophilia and hypofibrinolysis, post-chemotherapy or post-radiation therapy in cancer treatment, acute lymphoblastic leukaemia or human immunodeficiency virus (HIV) infection[1]. Risk factors for osteonecrosis are frequently based on anecdotal evidence and case-control studies, which complicates the establishment of definitive causal relationships[1].

Multifocal osteonecrosis is an uncommon condition in which corticosteroid exposure and chronic heavy alcohol consumption constitute the two principal non-traumatic etiologies[9]. Although both mechanisms lead to multifocal disease, they differ markedly in anatomical distribution and clinical course. Steroidinduced osteonecrosis is typically more extensive, bilateral, and symmetric, most frequently affecting the hips and knees, and tends to progress rapidly as a result of systemic vascular injury and disturbances in lipid metabolism[9]. In contrast, alcohol-related osteonecrosis more often presents with predominant femoral and knee involvement, follows an asynchronous or slower progression, and is attributed to ethanol-induced dyslipidemia and direct osteocytic toxicity[9].In this paper, we provide a brief overview of the underlying aetiologies associated with osteonecrosis, describe a case of an exceptionally extensive manifestation of osteonecrosis that illustrates the challenges in identifying the underlying cause in clinical practice, and present a flow diagram designed for use in clinical settings to systematically investigate all known potential underlying causes of osteonecrosis.

CASE REPORT

A female in her early forties presented at our outpatient clinic with pain on the dorsum of the right foot since a few months without prior trauma. This pain radiated upward to her lower leg and knee. The intensity of the pain was contingent upon physical activity, and with a tendency for some swelling at the ankle by the end of the day. The patient did not report any pain at rest. No apparent self-observed instability was present. The patient previously consulted a podiatrist, who had not initiated any treatment yet. Her general practitioner interpreted the symptoms as gout, but concurrent colchicine treatment was not successful. Medical history included asthma, cured right sided Achilles tendon tendinitis, and previous anaemia (e causa ignota) necessitating iron infusions. When specifically questioned by the orthopaedic surgeon the patient did not report any chronic alcohol or other substance abuse. However, she did admit to smoking approximately ten cigarettes a day. No (family) history of autoimmune diseases were noted. A negative family history for osteonecrosis or related conditions was also found. Furthermore, the patient did not use any medication.

Clinical examination revealed an intact medial arch of the right foot with slight valgus alignment of the heel bone. No skin abnormalities or swelling at the ankle was observed. The talocrural joint had a pain free and full range of motion. The Silfverskiöld test was negative. The subtalar joint exhibited tenderness, without a decrease in range of motion or increased talar tilt compared to the contralateral site. There were no clinical signs of Chopart or Lisfranc joint abnormalities. Upon palpation, there was noticeable tenderness present at the medial malleolus. On the lateral and medial aspects of the foot, tendons were diffusely painful upon palpation.

Radiographs of the right foot and ankle showed no abnormalities (Figure 1). Given the mild symptoms, absence of prior trauma or alarm symptoms, and normal radiographic findings, serious pathology was not anticipated, and further imaging was deemed unnecessary.

Consequently, a watchful waiting approach was adopted, with the anticipation that these enthesopathy-like symptoms would resolve over time. The patient returned to the outpatient clinic seven months later with worsening of the symptoms. Consequently, further investigation was carried out using magnetic resonance imaging (MRI).

An MRI of the right foot and ankle was conducted and showed multiple bone infarction sites in the distal fibula and tibia, extending to the subchondral plate of the tibiotalar joint, which exhibited a mild joint

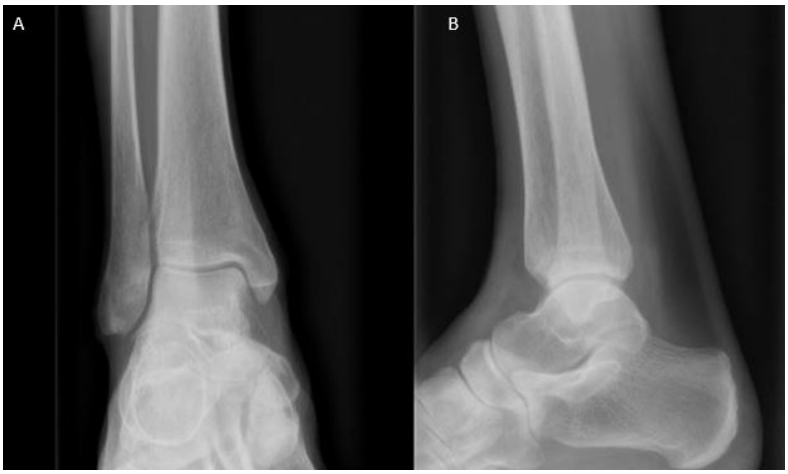

Fig. 1 — Conventional coronal (A) and lateral (B) radiographs of the right ankle, obtained at the moment of initial presentation showed no osseous abnormalities.

effusion (Figure 2). Multifocal infarction zones were observed in the midfoot region as well, including the navicular bone and the three cuneiform bones, as well as the base of the fourth and fifth metatarsals (Figure 3). The cuboid and calcaneus appeared unaffected. There were no signs of active tendinopathy. All ankle ligaments appeared to be in good condition. An additional skeletal scintigraphy was performed to investigate whether any other foci were present, and it revealed a similar pattern in the left ankle and foot, as well as in both knee regions including the patella (Figure 4). No activity corresponding to infarctions sites were noted elsewhere in the skeletal system.

Due to the prior history taking with the orthopaedic consultant only uncovering smoking as a risk factor, the patient was referred to internal medicine for further analysis. Specifically, additional laboratory analysis to rule out more distinct underlying pathology. The tests revealed elevated ferritin levels (618 microgram/l) with increased transferrin saturation (57%), indicative of hemochromatosis. Furthermore, it showed elevated liver enzymes, particularly gamma-glutamyl transferase (gammaGT) (428 units/litre) and aspartate aminotransferase (ASAT) (52 units/litre), which was potentially related to hemochromatosis. Combined dyslipidaemia with elevated cholesterol (6.5 mmol/litre), LDH-cholesterol (3.9 mmol/litre) and triglyceride (2.04 mmol/litre) were noted. The haemoglobin was 9.2 mmol/litre with an increased mean cell volume (MCV) of 103 femtolitre. No evidence of folate or vitamin B12 deficiency was found. The internal medicine consultant questioned the patient once again about chronic alcohol consumption as potential alcohol abuse corroborated with the laboratory findings. However, the patient insisted this was not the case.

As the diagnosis remained elusive, a vast array of testing was performed for auto-immune antibodies indicative for generalized auto-immune disease which all came back negative, including testing for HIV. Deoxyribonucleic Acid (DNA)-analysis was done to investigate hereditary hemochromatosis, however, these results were negative. Furthermore, testing for Thalassemia and Gaucher disease was performed, which also came back negative.

A dual x-ray absorptiometry (DEXA) scan showed osteopenia of the left hip, but no signs of osteoporosis. An ultrasound of the liver was performed which showed a mildly enlarged liver with signs of steatosis hepatis. Both these findings could be consistent with alcohol abuse, yet history taking performed by two separate specialists had not uncovered this as a viable

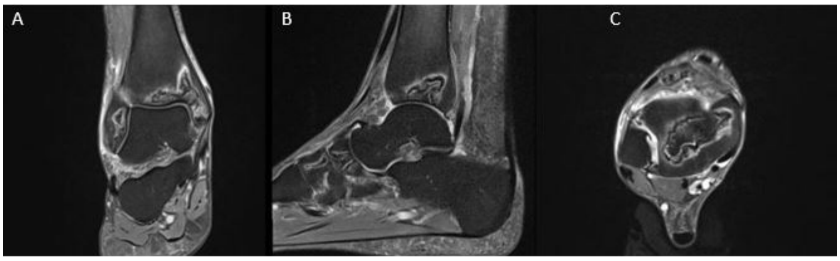

Fig. 2 — An MRI of the right ankle and foot was obtained seven months after the onset of symptoms.
The T2-weighted coronal (A), sagittal (B) and transversal (C) images of the ankle show multiple bone infarction sites in the distal fibula and tibia around the lateral and medial malleolus. This extends to the subchondral plate of the tibiotalar joint. Mild joint effusion is observed around these infarction sites as well.

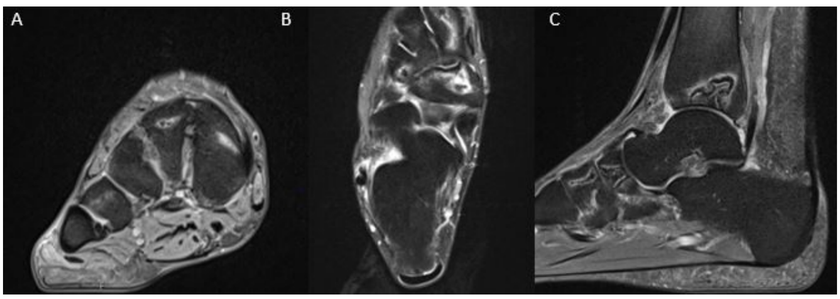

Fig. 3 — An MRI of the right ankle and foot was obtained seven months after the onset of symptoms.
The T2-weighted transversal (A), coronal (B) and sagittal (C) images of the foot show multifocal infarction zones in the midfoot region, including the navicular bone and the three cuneiform bones.

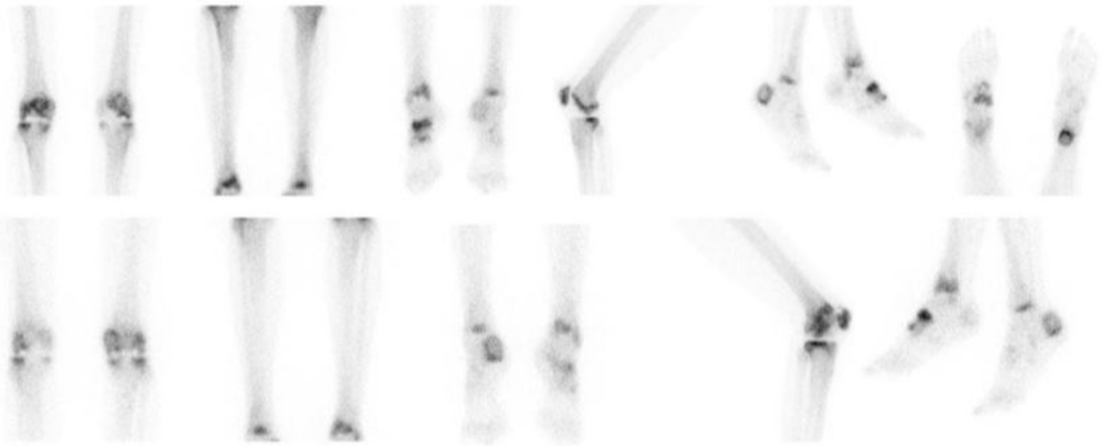

Fig. 4 — Bone scintigraphy of both the ankles, feet, and knees.
The bone scintigraphy scan shows osteonecrosis bilaterally. This includes the previously identified osteonecrosis of the right medial and lateral malleolus, navicular and cuneiform bones which is now also present on the left. Additionally, the calcaneus has decreased perfusion on both sides. Furthermore, both lateral and medial tibia plateau regions show infarction zones, as well as both patella and lateral and medial condyles of the femoral bones.

risk factor[8]. Consequently, the patient was referred to the local university hospital for more specialized follow-up including more specialized diagnostics at the internal medicine department.

Many potential causes for osteonecrosis were considered in the search for the underlying cause.

Firstly, medication usage was thoroughly reviewed. At the time of presentation, the patient was not using any medication. There was also no history of long-term or high dose glucocorticoid use. However, these were previously used short-term in a low dosage, several years before symptom onset. The patient had never taken bisphosphonates and there was no previous malignancy, therefore ruling out exposure to chemotherapy or radiotherapy.

Secondly, lifestyle-related risk factors were taken into consideration. The patient had no history of trauma or activities resulting in repetitive trauma, nor had she engaged in deep-sea diving. She reported smoking up to ten cigarettes a day and stated repeatedly that she did not consume alcohol regularly. There was no history of drug (ab)use.

Thirdly, less common disease entities that could potentially contribute to developing osteonecrosis at multiple locations were taken into consideration. There was no history of osteoporosis or transplant surgery. Furthermore, no other relevant medical conditions were identified in the patient's medical history. Thorough questioning about other symptoms did not yield any additional suspicions. Subsequent comprehensive analyses at the department of internal medicine and rheumatology ruled out pathologies potentially underlying osteonecrosis such as: HIV, sickle cell disease, hereditary osteonecrosis, hereditary thrombophilia, hypofibrinolysis, Thalassemia, Gaucher disease and hereditary hemochromatosis.

To conclude the patient was suffering from a multifocal osteonecrosis of both legs. Considering all factors, the sole identified risk factors were short-term low dose prior corticosteroid usage for no longer than a week and smoking. This presentation of multifocal osteonecrosis could also fit with chronic alcohol consumption. Combined with the laboratory results and imaging, it was indicative of a multifocal osteonecrosis caused by a systemic disease or factor. However, despite the history taking by up to four specialists and the extensive investigation, a conclusive diagnosis remained unclear.

During the extensive medical evaluation to identify an underlying cause, the patient presented at the emergency department after a fall. The incident involved her falling while walking towards her vehicle. Upon presentation the patient was suffering from pain in the left hip, radiographs of hip and pelvis showed no fractures. Additionally, the patient appeared to be intoxicated. After a conversation with the patient, she admitted having a history of alcohol abuse, however she insisted that this was no longer the case. During follow-up a computed tomography-scan (CT) was performed due to persisting pain, which showed a left-sided ramus superior fracture. Weightbearing as tolerated was allowed and oral analgesics were prescribed. The CT-scan additionally confirmed a stage 2 Ficat bilateral osteonecrosis of both femoral heads (Figure 5).

A follow-up MRI of the pelvis, both legs and both feet was performed. This MRI showed multiple new proximal femoral bone infarctions with involvement of the left and right trochanter major with bone marrow oedema. Additionally, both femoral heads showed signs of osteonecrosis which was classified as a stage 3 Ficat (Figure 6). There were no fractures or signs of collapse of the bony structures. Furthermore, the earlier findings of bone infarctions in the right and left lower extremities were conform the MRI earlier described.

In Table I an overview is provided of the affected bones and joints with the corresponding Ficat-arlet stage[10].

After the patient presented at the emergency department, a more elementary cause for the osteonecrosis was thus uncovered. As mentioned before, the test results such as elevated liver enzymes and hepatic steatosis observed on the liver ultrasound (as described in the investigations), the multifocal osteonecrosis, and the patient's intoxicated presentation at our emergency department, suggested chronic alcohol abuse.

An in-depth conversation with the patient followed at several consults after this incident. She remained adamant that she had not been drinking alcohol chronically for several years before she started suffering with symptoms of osteonecrosis.

Although the clinical history and emergency-department presentation raised strong suspicion for chronic heavy alcohol use, the most specific dedicated alcohol biomarker (carbohydrate-deficient transferrin (CDT)) was not available for this patient. The absence of this test limits the ability to objectively confirm chronic heavy drinking. CDT has been shown to be more specific than GGT for detecting heavy alcohol consumption, although sensitivity is imperfect and can be influenced by comorbid conditions such as nutritional status[11]. Thus, while the clinical picture is highly suggestive of alcohol-related osteonecrosis in this case, a definitive diagnosis of chronic alcohol misuse based on laboratory biomarkers cannot be made retrospectively, yet a more extensive biomarker panel could have aided the diagnostic process[11].

Due to the relative acute onset and progression of osteonecrosis in this relatively young patient, we referred the patient to the university hospital emergently. After the MRI, we advised core decompression of the femoral head and if the osteonecrosis were to advance rapidly, total hip replacement should be considered. Additionally, the investigation into etiology was to be extended.

Unfortunately, we do not have access to the medical records of the university to report further follow-up and treatment.

DISCUSSION

In this report, we present a case of a female patient in her early forties with an exceptionally extensive manifestation of osteonecrosis, with bilateral involvement across several major joints and bone regions, including the proximal femur, distal femur,

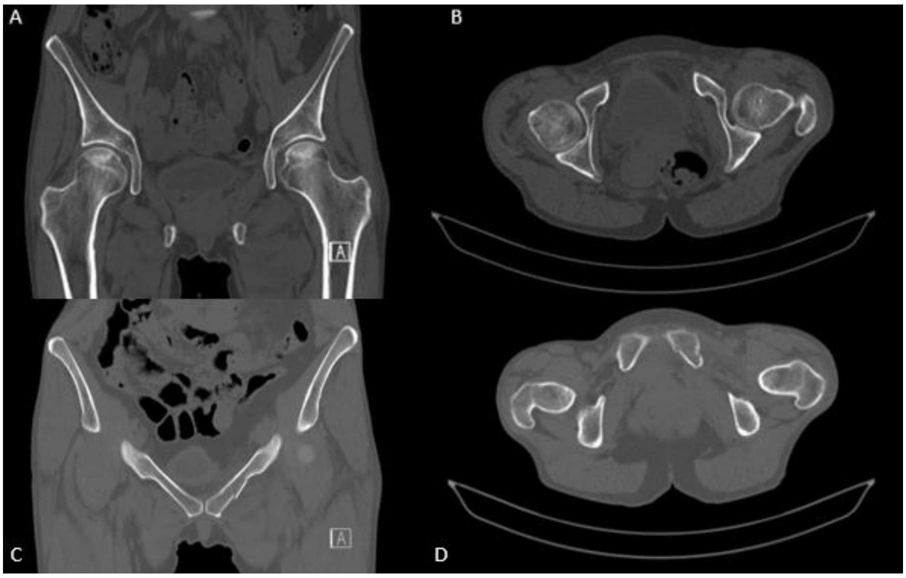

Fig. 5 — CT-scan of the pelvis and proximal femora was obtained after the intoxicated presentation on the emergency department with posttraumatic groin pain.
The CT-scan of the pelvis shows symmetrical ring-shaped sclerotic abnormalities in the subchondral regions of the femoral head on both sides, in the anteroposterior view (A) and axial view (B). No subchondral cysts or articular collapse is present. Additionally, a fracture of the ramus superior is seen on the left in a near anatomic position in the anteroposterior view (C) and axial view (D).

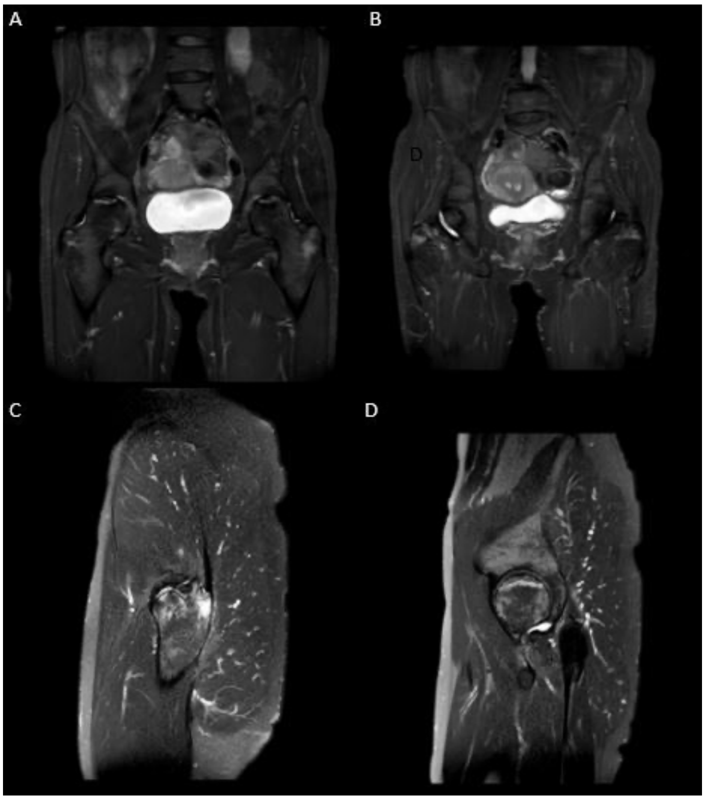

Fig. 6 — An MRI of the pelvis, including both femoral heads.
This MRI shows the pelvis in an antero-posterior view (A, B) and a sagittal view of the right hip (C, D).
In the antero-posterior imaging osteonecrosis can be seen of both femoral heads which was classified as Ficat stage-3 (A). Additionally, osteonecrosis of both throchanter major areas can be seen (B).
In the sagittal view, the right hip is shown (C, D). This shows diffuse areas of osteonecrosis in the throchanteric area (C) and the femoral head (D).

proximal tibia, patella, and the foot/ankle area. Such a widespread pattern suggests a severe systemic compromise in blood flow, leading to ischemic bone damage.

Following a comprehensive medical history and physical examination, an extensive array of diagnostic investigation was undertaken to identify the underlying pathology responsible for this widespread osteonecrosis. Initially, alcohol abuse was ruled out based on the patient's account. However, after the patient presented at our emergency department in an intoxicated state, it became evident that alcohol abuse could have been a contributing factor. Retrospective analysis of laboratory values and previous liver ultrasound findings corroborated the diagnosis of alcohol abuse.

Multifocal disease is relatively uncommon, occurring in approximately 3–5% of osteonecrosis cases, and thus warrants careful evaluation for systemic etiologies[12]. Among nontraumatic causes, chronic corticosteroid exposure and sustained heavy alcohol consumption are the two most frequently implicated factors. In many cohorts, corticosteroid use represents the predominant etiologic association (up to 91%), with alcohol misuse identified as the other principal contributor[12]. Reports of alcohol-induced multifocal osteonecrosis, however, remain scarce. Nevertheless, our case, characterized by suspected chronic alcohol misuse and predominant knee involvement, closely resembles previously described alcohol-related multifocal presentations[11-13].

It is estimated that up to 111 million of the worldwide populations suffers from an alcohol abuse disorder, defined as a physical and/or mental dependancy[14]. Alcohol abuse is a difficult topic to talk about and in this case the patient decided to conceal the discussion surrounding her (previous) drinking habits. If these habits were spoken of in an earlier stage, many invasive, costly and time-consuming tests could be avoided. To conclude, this led to redundant testing, which is unfortunate and not cost-effective. Chronic alcohol abuse can be detected through various methods. In this report, laboratory results and follow-up liver ultrasound indicated signs consistent

Table I. — Overview of anatomic structures in which osteonecrosis was found.
Classified according to the modified Ficat-arlet classification. The classification is mostly used for defining osteonecrosis at the hip, but may be used over different locations.The classification is generally defined as: Stage 0: normal radiographs/CT/MRI, no clinical symptoms; Stage 1: normal radiograph, bone oedema on MRI, increased bone tracer on bone scan, minor pain of affected anatomical site; Stage 2: radiograph showed osteopenia or bone cysts and/or sclerosis, geographical changes op MRI, increased uptake on bone scan, pain and stiffness of affected anatomical site; Stage 3: radiographic crescent sign (subchondral lucency), bone collapse with joint preservation on MRI, pain and stiffness with possible limping; Stage 4: end stage osteonecrosis on radiographic imaging, joint collapse on MRI, severe joint pain (10).

Affected bone/joint	Clinical symptoms	Imaging findings	Ficat-arlet classification
Right distal fibula	Pain and stiffness	Radiographic imaging: no abnormalities MRI: bone infarction, no collapse (Figure 2)	Stage 2
Right distal tibia	Pain and stiffness	Radiographic imaging: no abnormalities MRI: bone infarction, no collapse (Figure 2)	Stage 2
Right base of the metatarsals[4,5], cuneiform bones, navicular bone	Pain and stiffness	Radiographic imaging: no abnormalities MRI: bone infarction, no collapse (Figure 3)	Stage 2
Right and left knee joints	Pain and stiffness	Skeletal scintigraphy: increased uptake (Figure 4) MRI: bone infarction, no collapse.	Stage 2
Right and left femoral head	Pain and stiffness	CT: subchondral oedema and cysts, no collapse (Figure 5) MRI: bone collapse with joint preservation (Figure 6)	Stage 3

with chronic alcohol abuse. However, these signs alone are insufficient for a definitive diagnosis. It is advisable that in the diagnostic work-up for elusive cases of osteonecrosis, physicians consider including markers indicative of chronic alcohol consumption, such as carbohydrate-deficient transferrin (CDT) and gammaGT[15]. These markers are frequently elevated in the serum of individuals who consume alcohol, suggesting their potential inclusion in the routine assessment, especially since blood sampling is a standard part of diagnostic procedures. These markers could facilitate the diagnostic process in cases where patients might be untruthful or provide an opportunity to initiate a discussion about alcohol consumption with the patient. However, the sensitivity and specificity for both markers are not high enough to make a definitive diagnosis, which is why they have not been universally adopted in clinical settings[16]. This is particularly true for patients with a high body mass index or comorbidities that affect CDT and gammaGT levels[17]. Consequently, the diagnosis of chronic alcohol abuse continues to rely on patient interviews.

Multifocal osteonecrosis, such as in this case, is a rare condition. Approximately 3% of osteonecrosis cases are multifocal, with an estimated of 5.3% attributed to chronic alcohol consumption based on a single cohort study[18,19]. Currently, only several case reports have been published of multifocal osteonecrosis related alcohol ingestion and the precise prevalence of alcohol abuse as a causative factor for multifocal osteonecrosis remains uncertain[13,20]. Given the diagnostic complexities involved, an osteonecrosis identifying algorithm is proposed in figure 7 to assist clinicians in navigating this process. When reflecting on the current presented case, step one of the algorithm to ‘evaluate lifestyle factors’ was potentially not investigated to its full potential. This led to all the following steps being investigated thoroughly without a diagnosis. With this tool, the goal is to aid clinicians to investigate the cause for osteonecrosis in a systematic manner.

In conclusion, chronic alcohol consumption as a sole causative factor for extensive multifocal osteonecrosis is rare. However, after thorough analysis, no other explanations for the extensive osteonecrosis in our patient case were found beyond alcohol use and smoking. An essential step in the treatment strategy for progressing multifocal osteonecrosis is the removal of the underlying osteonecrotic factors. Unfortunately, we only discovered the patient’s alcohol use at a later stage, which limited our ability to address it sooner. Despite inquiries from various specialists at different times, we did not receive realistic answers in earlier phases. This highlights the importance of critically assessing alcohol consumption, even in patients where alcohol misuse is not initially suspected. It is crucial to explain to patients, without judgment, why this information is being sought and the significance of accurately reporting alcohol intake in cases of multifocal osteonecrosis. However, that this young, previously healthy patient developed such extensive osteonecrosis remains an uncommon occurrence which is not yet fully understood.

Ethics statement: The author reports no conflict of interest and no financial support for this work. The patient provided written informed consent for publication of the case details, radiographic imaging, and laboratory data, with all personal identifiers removed.

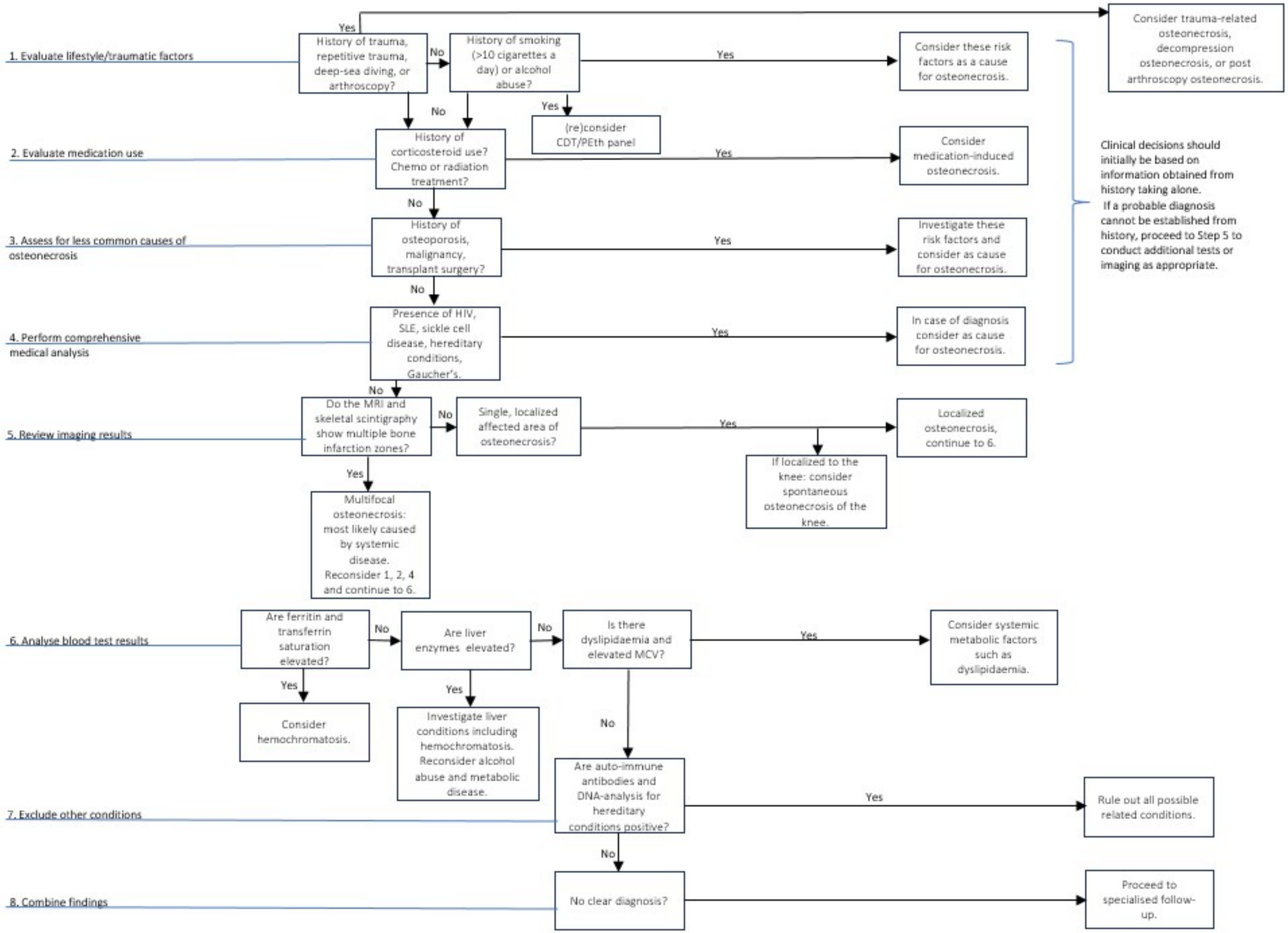

Fig. 7 — Flowchart to aid in identifying the underlying cause of osteonecrosis in patients.
Ensure to not do any imaging and or blood work that is not indicated, Consider a full work-up with blood samples and additional imaging, only if there is a clear indication for this. Risk factors and lifestyle factors are not enough to make a definitive diagnosis. (CDT; Carbohydrate-Deficient Transferrin, PEth; phosphatidylethanol, HIV; human immunodeficiency virus, SLE; systemic lupus erythematosus, MRI; magnetic resonance imaging, MCV; mean cell volume, DNA; Deoxyribonucleic Acid).

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