High Prevalence of Prothrombotic Abnormalities in Multifocal Osteonecrosis

Description of a Series and Review of the Literature

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Abstract: Multifocal or multiple osteonecrosis (ON), defined by the involvement of 3 or more anatomic sites, is unusual, being observed in only 3%–10% of patients diagnosed with ON. We report the clinical characteristics of a cohort of 29 patients with multifocal ON from a single center and evaluate the prevalence of associated prothrombotic abnormalities in 26 of these patients. We conducted a retrospective study of all patients diagnosed with multifocal ON evaluated in our institution during the last 20 years. We recorded clinical manifestations and underlying diagnoses. A wide thrombophilic profile was performed, including antithrombin, protein C, protein S, lupus anticoagulant, anticardiolipin antibodies, activated protein C resistance, factor V Leiden, mutation G-20210-A of the prothrombin gene, and factor VIII. Coagulation test results were compared with those in a healthy control group and a group of patients with history of lower-extremity deep venous thrombosis.

The mean age of the patients was 49.2 ± 15 years (range, 28–81 yr). The mean number of ON localizations per patient was 5.2 ± 2.3 (range, 3–11). Hips were the most commonly affected joint (82%), followed by knees (58%), shoulders (37%), and ankles (13%). Most patients had an underlying disease process, and 12 of 25 (48%) patients had coagulation test abnormalities. The most common alterations were high factor VIII levels and antiphospholipid antibody (aPL) positivity in 24% and 20% of cases, respectively. These abnormalities were more prevalent in patients with multifocal ON compared with patients in the control groups.

Sixty-one percent of patients had a history of corticosteroid treatment. Patients with coagulation abnormalities had a higher number of ON localizations per patient (6.5 ± 2.7 vs. 3.88 ± 0.8; p = 0.002) and a higher prevalence of atypical ON localizations (25% vs. 0%; p = 0.05).

In conclusion, in the present cohort of patients with multifocal ON, 48% of the patients had at least 1 prothrombotic factor, especially high levels of factor VIII and aPL. These findings have major implications for the diagnosis and treatment of multifocal ON and clearly indicate the need to perform a thrombophilic profile in these patients.

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Abbreviations: aCL = anticardiolipin antibodies, aPL = antiphospholipid antibodies, APS = antiphospholipid syndrome, aPTT = activated partial thromboplastin time, DVT = deep venous thrombosis, ELISA = enzyme-linked immunosorbent assay, HIV = human immunodeficiency virus, LA = lupus anticoagulant, Lp(a) = lipoprotein (a), MRI = magnetic resonance imaging, MTHFR = methylenetetrahydrofolate reductase, ON = osteonecrosis, PAI-1 = plasminogen activator inhibitor, PT = prothrombin time, SLE = systemic lupus erythematosus.

INTRODUCTION

Osteonecrosis (ON), also known as avascular necrosis of bone, is the result of an interruption in blood circulation. This leads to a disparity between the oxygen requirements of the bone cell and the ability of the local circulation to supply the need, leading to bone and bone marrow cell death, which may finally result in mechanical failure and joint destruction.

A variety of traumatic and nontraumatic factors have been implicated in the pathogenesis of ON. Corticosteroid use and excessive alcohol intake are the main nontraumatic factors related, accounting for more than 90% of cases.[4] Other processes, such as decompression disease (Caisson disease), human immunodeficiency virus (HIV) infection, radiation therapy, inheritable COL2A1 gene mutations, Gaucher disease, or sickle cell hemoglobinopathies, among others, have been associated with the development of ON.[26] In relation to the intrinsic nature of this process, several prothrombotic conditions have been evaluated and described in patients with ON, including antiphospholipid antibodies (aPL),[25] factor V Leiden,[19] protein C deficiency,[9,22] protein S deficiency,[9] hyperhomocysteinemia,[5] methylenetetrahydrofolate reductase (MTHFR) mutations,[6] elevated factor VIII levels,[21] and elevated plasminogen activator inhibitor,[17] among others.[24] Indeed, histologic findings in nontraumatic ON usually reveal thrombosis of terminal arteries in subchondral bone, which, due to the few collaterals of these arteries, can trigger progressive involvement of venules, veins, and arterioles.[4,24]

Multifocal or multiple ON, defined by the involvement of 3 or more anatomic sites, is unusual, being observed in only 3%–11% of patients diagnosed with ON.[18,34] This process can affect any skeletal bone, with particular involvement in the femur, tibia, and talus, and has been associated mainly with a previous history of high-dose corticosteroid therapy, alcohol consumption, and systemic disorders such as systemic lupus erythematosus (SLE), solid organ transplantation, and hematologic diseases. Nevertheless, a few studies have indicated that this process may also be associated with hypercoagulation disorders or a hypofibrinolysis state, further suggesting the convenience of evaluating the presence of prothrombotic abnormalities in these patients.[17,24,27,34]

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Therefore, we conducted the present study to analyze the clinical characteristics of and the prevalence of prothrombotic abnormalities in patients with multifocal ON and to review the literature related to this subject.

METHODS

Patients

We performed a retrospective study including all patients with a diagnosis of multifocal ON evaluated in our department over the 20-year period from 1990 to 2010. Clinical data were obtained from a detailed review of the medical records, with special reference to history of risk factors for ON, corticosteroid treatment, and associated clinical conditions. Clinical manifestations, location, and evolution were recorded in all patients.

Radiologic (including plain X-ray, computed tomography [CT] scan, and/or magnetic resonance imaging [MRI]) and scintigraphic results were recorded in all patients. Diagnosis of ON was established by compatible radiographic study, and diagnosis of multifocal ON was established by involvement of 3 or more anatomic sites.

Thrombophilic Profile

All patients with multifocal ON attended in our department from 1990 to 2010 were evaluated with a standardized protocol for analyzing procoagulant conditions through an extensive thrombophilic profile.

The thrombophilic profile included the following: prothrombin time (PT), activated partial thromboplastin time (aPTT), plasma fibrinogen, functional antithrombin, functional protein C, free protein S, total protein S, plasminogen, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), activated protein C resistance, factor V Leiden, mutation G-20210-A of the prothrombin gene, and coagulation factor VIII.

PT and aPTT were determined in an automated BCS XP analyzer (Siemens, Marburg, Germany) using standard reagents (Thromborel and Actin FS, Siemens). Fibrinogen was measured by the Clauss technique. Protein C activity was quantified by a colorimetric assay (Chromogenix IL, Milano, Italy). Free and total protein S were quantified by enzyme-linked immunosorbent assay (ELISA) (Stago, Asnières, France). Antithrombin and plasminogen activity were measured using chromogenic assays (Siemens). Platelet function testing was done by transmission light aggregometry in platelet-rich plasma using adenosine diphosphate (ADP) and epinephrine as agonists. The diagnosis of "sticky platelet syndrome" was established by evidence of hyperaggregability of platelets in platelet-rich plasma with ADP, epinephrine, or both measured as preservations of the response to the referred agonists at very low concentrations.[36] Factor V Leiden and prothrombin gene G20210A mutations were determined by real-time polymerase chain reaction (PCR) (Roche, Mannheim, Germany). Coagulation factor VIII was determined using a chromogenic assay (Chromogenix). The normal range of factor VIII in our laboratory is 65–135 IU/dL. Lupus anticoagulant was detected following the guidelines of the International Society on Thrombosis and Haemostasis: the diluted Russell viper venom test (dVVT) and diluted aPTT were employed for the screening, and dilution (1:1) in normal plasma tests and dVVT after the addition of an excess of phospholipids were used for confirmation. Anticardiolipin antibodies were measured by a standardized ELISA according to the international standards of IgM (MPL) and IgG phospholipid units (GPL) (Cheshire Diagnostics, Chester, UK).

All patients with positive LA and/or aCL were confirmed by at least 2 determinations separated by 12 weeks according to international recommendations at that time.[40] Factor VIII was considered to be elevated in cases with levels above the 98th percentile of levels determined in blood donors (>200 IU/dL).[52]

For comparisons in the thrombophilic profile, a control group of 200 healthy individuals and a group of 100 patients with first lower-extremity deep venous thrombosis (DVT) were selected. These patients and the healthy blood donors were consecutively recruited in our institution in a separate case-control study on thrombophilia parameters in DVT.

Statistical Analysis

All data are expressed as mean ± SD. The Student t test and the nonparametric Kruskal-Wallis test were used to compare differences for continuous variables. Differences between proportions were assessed with the chi-square test, and the Fisher exact test was used when appropriate. A p value <0.05 was considered statistically significant.

With a 2-sided α of 0.05 and a statistical power of 90%, we estimated that a sample of 200 healthy controls was needed to detect a difference of 20% in proportions for coagulation abnormalities among ON patients and controls.

Literature Review

Additionally, we carried out a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) literature search to locate all reports of multiple ON and prothrombotic abnormalities published in English since 1961 when initial reports indicated a possible association.

RESULTS

General Characteristics

Of the 29 patients with multifocal ON included in the study, the thrombophilic profile was performed in 25 patients. In 4 patients coagulation profile tests were not undertaken: 2 patients were not available for study, 1 patient died, and in 1 case (a patient with sickle cell disease) the tests were not performed because the cause of ON was attributed to the underlying disease. The mean current age was 49.2 ± 15 years (range, 28–81 yr), and 69% of the patients were men. The general clinical characteristics of the patients included are shown in Table 1. Sixty-one percent of the patients had a previous history of high or maintained doses of corticosteroids. The main underlying disorders were HIV in 7 (24%) patients; lymphoproliferative disorders in 6 (21%), 3 of whom had undergone a previous bone marrow transplant; orthotopic liver transplantation in 4 (14%) patients; primary antiphospholipid syndrome (APS) in 3 (10%); and dermatomyositis in 2 (7%) patients. Other conditions were found in 1 case each including renal transplant, sickle cell disease, chronic obstructive pulmonary disease, and autoimmune hepatitis. One patient had a previous history of spontaneous hemorrhage, and 4 patients had no underlying disease (idiopathic ON). In 2 patients 2 comorbidities potentially related to the development of ON were detected: prolactinoma plus APS in 1 patient and mastocytosis plus acute myeloid leukemia in the other.

Coagulation Abnormalities

Coagulation abnormalities and clinical outcomes are summarized in Table 2. Briefly, 12 (48%) of 25 patients showed abnormalities on coagulation tests: 11 (44%) patients had 1 alteration, and 2 (8%) had 2 alterations. The most common alterations were high factor VIII levels (>200) in 6 (24%) patients and aPL positivity (LA and/or aCL) in 5 (20%) patients. Interestingly, 8 (27.6%) patients had a previous history of DVT, but only 1 had

TABLE 1. General Characteristics of 26 Patients With Multifocal Osteonecrosis

Patient	Sex/Age (yr)	Underlying Diseasea	Previous Corticosteroid Use	Maximum Prednisone Dose (mg/kg)	Duration (mo)	Abnormal Coagulation Test	Outcome
1	F/72	Liver transplantation	Yes	>1	7	Yes	Death
2	F/62	COPD	Yes	1	NR	No	Alive
3	M/38	Liver transplantation/ primary APS	Yes	>1	9	Yes	Alive
4	F/81	Dermatomyositis	Yes	1	NR	Yes	Alive
5	M/32	Bone marrow transplant	Yes	1	12	Yes	Alive
6	F/77	Dermatomyositis	Yes	1	48	Yes	Alive
7	M/48	HIV	No			Yes	Alive
8	M/58	Bone marrow transplant	Yes	1	3	No	Alive
9	F/28	Bone marrow transplant	Yes	1	NR	No	Alive
10	M/62	Kidney transplant	Yes	1	NR	No	Alive
11	M/51	Previous prolactinoma/ primary APS	Yes	Postsurgery (NR)	NR	Yes	Alive
12	M/57	Mastocytosis/acute myeloid leukemia	Yes	>1	NR	No	Death
13	M/54	None	No			No	Alive
14	M/31	Lymphoma	Yes	1	6	No	Alive
15	M/55	None	No			No	Alive
16	M/52	HIV	Yes	1	NR	Yes	Alive
17	M/41	HIV	No			No	Alive
18	M/51	HIV	No			Yes	Alive
19	M/53	Primary APS	No			No	Alive
20	M/34	None	No			Yes	Alive
21	F/43	HIV	No			Yes	Death
22	M/50	HIV	No			No	Alive
23	M/33	Sickle cell disease	No			ND	Alive
24	F/32	HIV	Yes	1	>12	No	Alive
25	M/30	Autoimmune hepatitis	Yes	1	NR	No	Alive
26	M/33	Acute myeloid leukemia	Yes	1	12	Yes	Alive

Abbreviations: COPD = chronic obstructive pulmonary disease, ND = not determined, NR = not recorded.

abnormal coagulation tests (1 with APS). Sixty-one percent of patients with coagulation abnormalities had a previous history of corticosteroid therapy, and 4 of 7 patients with HIV also had coagulation test abnormalities. All HIV patients were under high active antiretroviral therapy, including protease inhibitors.

As shown in Table 3, patients with multifocal ON had a statistically significant higher prevalence of aPL and elevated factor VIII compared with patients with DVT and healthy controls. Conversely, patients with DVT tended to have a higher prevalence of Factor V Leiden and prothrombin G20210A gene mutation than patients with multifocal ON.

Clinical Features and Outcome

The mean number of bones affected with ON per patient was 5.2 ± 2.3 (range, 3–11). Patients with coagulation abnormalities had a higher number of ON-affected bones (6.5 ± 2.7 vs. 3.8 ± 0.8; $p = 0.002$). Conversely, patients without coagulation abnormalities had a more frequent history of corticosteroid use (100% vs. 63%; $p = 0.05$). Patients with coagulation abnormalities had a higher prevalence of atypical localizations of ON (25% vs. 0%; $p = 0.05$), and additionally had a trend for more tibial involvement (50% vs. 15%; $p = 0.06$), compared with patients without coagulation abnormalities. There were no significant differences in terms of age, sex, other ON localizations, previous thrombosis, comorbidities, or arthroplasty requirement among patients with or without coagulation abnormalities (Table 4).

Four of the 5 patients with associated aPL received anticoagulation therapy (all with APS), and the remaining patient received antiaggregation therapy. In spite of anticoagulation treatment within the therapeutic international normalized ratio (INR) range, 2 patients developed a new episode of ON (Table 5). The remaining patients with other associated coagulation abnormalities were treated with low-dose aspirin, and no further ON episodes were observed.

Hips were the joint most commonly affected (82%; bilateral in 72.4% of cases), followed by the knees (58%; bilateral in 48%; Figure 1), shoulders (37%; bilateral in 24%), and ankles (13%; bilateral in 3.4%; Figure 2). Other common locations affected were the talus (17%; bilateral in 7%; Figure 3), and the calcaneus (10%). Vertebral involvement was uncommon, observed in only 1 case.

Sixteen of 26 (61.5%) patients followed underwent joint replacement surgery: 6 patients had single joint replacement, 9 patients had bilateral hip replacement, and 1 patient required 3 arthroplasties. Fifteen of 16 patients treated with arthroplasty had positive X-rays and signs of degenerative changes with Ficat stage IV; the remaining patient had Ficat stage III.

TABLE 2. Coagulation Abnormalities and Clinical Features

Patient	Coagulation Abnormality	Previous Thrombosis	No. of ON Sites	Arthroplasty Required	Surgery
1	Elevated factor VIII (223%)	No	9	No	
2	No alteration	No	3	No	
3	LA	Yes	11	Yes	Bilateral hip and right knee arthroplasty
4	Elevated factor VIII (202%)	No	7	Yes	Left hip arthroplasty
5	Leiden factor V mutation	No	9	Yes	Right hip arthroplasty
6	Elevated factor VIII (214%)	No	8	Yes	Right hip and right knee arthroplasty
7	aCL IgG (42 GPL), LA	No	6	Yes	Bilateral hip arthroplasty
8	No alteration	Yes	5	Yes	Bilateral hip arthroplasty
9	No alteration	No	3	No	
10	No alteration	Yes	4	Yes	Bilateral hip arthroplasty
11	aCL IgM (53 MPL)	No	9	No	
12	No alteration	Yes	3	No	
13	No alteration	No	3	No	
14	No alteration	No	5	No	
15	No alteration	No	4	Yes	Right hip arthroplasty
16	aCL IgG (86 GPL), LA, elevated factor VIII (229%)	No	6	Yes	Right hip arthroplasty
17	No alteration	Yes	4	Yes	Bilateral hip arthroplasty
18	No alteration	No	3	Yes	Bilateral hip arthroplasty
19	aPL	Yes	3	Yes	Bilateral hip arthroplasty
20	Low platelet aggregation response to ADP and arachidonic acid	No	5	No	
21	Elevated factor VIII (239%)	No	3	No	
22	No alteration	No	4	Yes	Bilateral hip arthroplasty
23	ND	No	10	Yes	Right hip arthroplasty
24	No alteration	Yes	5	Yes	Bilateral hip arthroplasty
25	No alteration	Yes	4	No	
26	Elevated factor VIII (211%) and sticky platelet	No	4	No	

At the study's end, 25 (86%) patients remained alive and 4 (14%) had died due to complications related to the underlying process (not related to ON or joint replacement surgery).

DISCUSSION

The present study shows a high prevalence of coagulation disorders in patients with multifocal ON, even in patients with other associated clinical conditions such as corticosteroid therapy and HIV infection. Literature regarding multifocal ON is limited. Clinical data from the largest cohorts published to date (including the present study) are summarized in Table 6.

Similar to previous studies, in the present series femoral head, humeral head, and distal femur were the ON locations most frequently affected. Nevertheless, multifocal ON may involve any bone location, including metacarpal[50] and tarsal bones[44] and ribs.[62] Since several patients with ON may follow an asymptomatic course, high clinical suspicion is important. Bone scan is considered the least expensive and most cost-efficient screening method for the initial assessment of suspected multifocal ON,[55] with a sensitivity and specificity of about 80% for the diagnosis of ON.[54,55] However, MRI is the most sensitive method for diagnosis.[42]

LaPorte et al[34] described one of the largest series of multifocal ON to date. The authors retrospectively reviewed a series of 1056 patients with ON, with only 32 (3%) having multifocal ON. The main disorders associated with multifocal ON were SLE (13 patients), inflammatory bowel disease (5 patients), neoplasia (4 patients), and renal transplantation (3 patients). Most patients were women (75%), with a mean age of 34 years. All patients had involvement of bilateral femoral heads, and 30 also had bilateral involvement of the knees. Other affected areas were the shoulders (78%), ankles (20%), elbows (9%), carpus (6%) and calcaneus (3%). The most common clinical presentation was polyarthralgia, including the hip syndrome, although 8 patients presented with isolated knee pain. Patients in the current study frequently reported previous corticosteroid therapy and showed similar bone involvement, with more than 60% requiring surgical joint replacement.

In 1999, the Collaborative Osteonecrosis Group[2] reported the results of a multicenter study that included 101 patients with multifocal ON collected in 21 centers during 16 years. In this cohort, hips were involved in all patients, and there was a bilateral predominance at all sites. Additionally, 89% of knees were affected, followed by the shoulders and ankles in 73% and 35% of cases, respectively. It is noteworthy that 12 (86%) of 14 patients tested for thrombophilia or hypofibrinolysis were found to have a coagulation disorder, including familial protein S deficiency, high tissue plasminogen activator inhibitor, and Factor V Leiden deficiency.

TABLE 3. Coagulation Abnormalities in Patients With Multifocal ON, Patients With DVT, and Healthy Controls

	Group A Multifocal ON (n = 25)* No. (%)	Group B DVT (n = 100) No. (%)	Group A vs. B P Value†	Group C Healthy Controls (n = 200) No. (%)	Group A vs. C P Value†
Mean age, yr (±SD)‡	49.2 ± 15	51 ± 14	0.127	49 ± 13	0.851
Male	19 (76)	41 (41)	**0.003**	76 (38)	<**0.0001**
Female	6 (24)	59 (59)		124 (62)	
Antithrombin deficiency	0 (0)	0	1.0	0 (0)	1.0
Protein C deficiency	0 (0)	3 (3)	0.50	0 (0)	1.0
Protein S deficiency	0 (0)	4 (4)	0.58	1 (0.5)	0.88
aPL	5 (20)	6 (6)	**0.04**	1 (0.5)	<**0.0001**
Elevated factor VIII	6 (24)	1 (1)	<**0.0001**	0 (0)	<**0.0001**
Platelet hyperaggregability	1 (4)	0 (0)	0.20	0 (0)	0.11
Factor V Leiden	1 (4)	16 (16)	0.19	6 (3)	0.56
Prothrombin G20210A gene mutation	0 (0)	13 (13)	0.069	5 (2.5)	0.55

*Coagulation tests were performed in 25 of 26 patients.

†P values in bold are signficant (<0.05).

‡Mean age at time coagulation tests were performed.

More recently, a French group[14] evaluated the clinical course of 200 patients with sickle cell disease over a period of 15 years with 87 patients having multifocal ON, affecting 455 sites. The most commonly affected areas were the proximal femur, followed by proximal humerus, distal femur, proximal tibia, distal tibia, and talus. The very high incidence of ON in this French series was probably related to the routine use of MRI and the particular characteristics of the cohort (sickle cell disease patients). Such a high percentage is not usually seen in other populations and clinical conditions. Indeed, 1 of the patients in the present series had sickle disease, with 8 vertebrae affected by ON; this was the only case of the series with this type of involvement.

Although the pathogenesis of nontraumatic ON is not well understood, several factors have been proposed, such as genetic factors, coagulation abnormalities including inherited and acquired thrombophilias, and hypofibrinolysis or even endothelial factors, among others, suggesting a multifactorial process.[3] Indeed, a 2010 case-control study[29] including 1450 patients with ON of the femoral head and 7250 controls demonstrated that patients with ON of the femoral head had an increased risk for the development of coronary heart disease during the first 3 years after the diagnosis of ON (HR, 1.43; 95% CI, 1.10–1.86). This increased risk was higher in males and in patients younger than 65 years of age. These data suggest that coagulation abnormalities and endothelial dysfunction involve not only bone tissue circulation but also other cardiovascular areas. On the other hand, 2 different studies[20,30] have demonstrated the association between polymorphisms of the endothelial nitric oxide synthetase gene with the development of idiopathic ON, probably related to a reduction in nitric oxide production.

The evaluation of diverse prothrombotic factors in patients with idiopathic ON has shown discrepant results. In a case-control study that evaluated several prothrombotic factors including aCL, anti-β2 glycoprotein I antibodies, S protein, antithrombin, mutation of factor V Leiden, G-20210-A mutation in prothrombin gene, lipoprotein (a) (Lp[a]), and mutation A223 V MTHFR, Mehsen and colleagues[37] did not find an increased frequency in any of these factors in patients with ON. On the other hand, Zalavras and colleagues[63] reported a high prevalence of the factor V Leiden mutation in a series of 74 patients with ON

TABLE 4. Patients With Multifocal ON, With or Without Coagulation Abnormalities

	Multifocal ON With Coagulation Abnormalities (n = 12)	Multifocal ON Without Coagulation Abnormalities (n = 13)	P
Mean age, yr (±SD)	51 ± 47	47 ± 12	0.49
Male sex (%)	66	77	0.56
Previous corticosteroids, %	63	100	**0.05**
HIV infection, %	25	30	0.74
Mean no. of ON	6.5 ± 2.7	3.8 ± 0.8	**0.002**
Five or more ON, %	66	0	<**0.001**
Hip involvement, %	83	84	0.94
Tibial involvement, %	50	15	0.06
Humerus involvement ,%	50	46	0.84
Astragalus involvement, %	33	21	0.56
Other location, %	25	0	**0.05**
Thrombosis, %	28	60	0.20
Arthroplasty, %	70	53	0.43
Death, %	18	15	0.85

TABLE 5. Follow-Up of Patients With Antiphospholipid Antibodies (aPL)

Patient	Symptoms Onset	Diagnosis of aPL	Date and Type of Treatment	New ON Episodes
1	September 2001	July 2005	Anticoagulation July 2005	Yes (1 episode of ON in 2006)
2	January 2001	May 2005	Antiaggregation June 2005	No
3	January 1984	October 2007	Anticoagulation October 2005	No
4	May 2004	July 2004	Anticoagulation July 2004	No
5	October 2008	January 1998	Anticoagulation January 1998	Yes (2 episodes of ON, 2009 and 2010) under anticoagulation

(23 idiopathic and 49 secondary ON). The prevalence of the factor V Leiden mutation was 18% in ON patients compared to 4.6% in the control group, with 21% prevalence in the idiopathic ON subgroup. Nevertheless, in the current study, we found only 1 case (4%) with the factor V Leiden mutation, similar to the expected prevalence of this mutation in the general Spanish population[15] and in our healthy control group. Conversely, this was the most frequent coagulation abnormality found in the present DVT group, being observed in 16% of the patients.

Glueck et al[21] compared measures of thrombophilia and hypofibrinolysis in 133 patients with idiopathic (n = 71) and secondary hip ON (n = 62) with measures in healthy control subjects. Hypofibrinolysis studies included plasminogen activator inhibitor (PAI-1) and Lp(a). The authors reported higher levels of factor VIII (>150%) and Lp(a) in patients with idiopathic ON, whereas in patients with secondary ON, high factor VIII, factor V Leiden heterozygosity, and resistance to activated protein C, were more frequently observed. Jones et al[27] also indicated a relationship between procoagulant factors and ON in a series of 45 patients with large joint ON: 82.2% of these patients had at least 1 procoagulant factor, compared with 30% of controls. The presence of high levels of aCL IgG and/or low levels of resistance to activated protein C was the most common alteration. Cenni and coworkers[7] evaluated several thrombotic and fibrinolytic factors in a 2011 case-control study including 18 patients with idiopathic ON, 18 patients with corticosteroid-associated ON, and 44 healthy controls; they observed significantly higher plasminogen activity in patients with idiopathic ON, a finding that was not observed in patients with corticosteroid-associated ON. The frequency of inherited thrombophilia (factor V Leiden, prothrombin gene mutation and genotypes 4G/5G and 4G/4G of the PAI-1) was similar to that of the controls.

In the current study, the most frequent prothrombotic abnormality was the increase in factor VIII levels, which was found in about one-quarter of patients. Conversely, no individual from the control group showed increased values of this factor, and only 1 patient with DVT had increased values. High levels of factor VIII have been recognized as an independent risk factor for DVT.[52] Indeed, patients with factor VIII levels >150 IU/dL had an almost 5-fold higher risk of thrombosis than those with normal levels (<100 IU/dL).[32] In addition, elevated factor VIII was shown to constitute a dose-dependent risk factor for DVT, with increases of 10% in the risk for first DVT for each 10 IU/dL increment in plasma factor VIII.[33] High factor VIII concentrations represent a risk factor for thrombosis similar to the deficiencies of inhibitors such as proteins C and S and activated protein C resistance.[59] The Austrian Study on Recurrent Venous Thromboembolism[33] demonstrated that the risk of recurrent thrombosis is 7-fold higher among patients with factor VIII levels exceeding the 90th percentile (>234 IU/dL), and this factor also constitutes a risk factor for the development of thrombosis in non-Western populations, as occurs in portal vein thrombosis and DVT in Indian[31] and Japanese[48] populations, respectively.

The role of factor VIII as a procoagulant factor has been debated by some authors interpreting its function as an acute phase reactant, with controversy as to whether factor VIII represents a congenital prothrombotic predisposition, an acquired

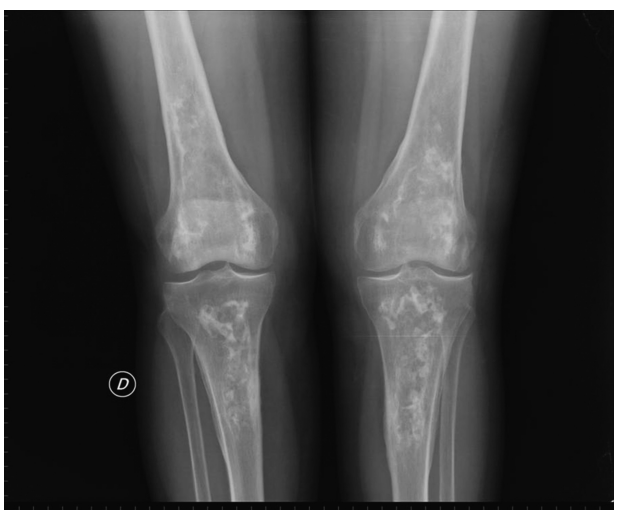

FIGURE 1. Bilateral knee X-rays showing extensive bilateral bone infarcts in the distal femur and proximal tibia. (''D'' indicates the right side.)

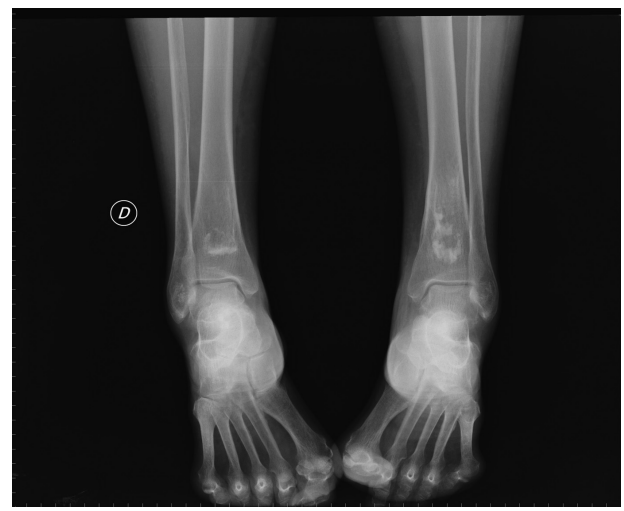

FIGURE 2. Bilateral ankle X-rays showing bilateral bone infarcts in the distal tibia and fibula. (''D'' indicates the right side.)

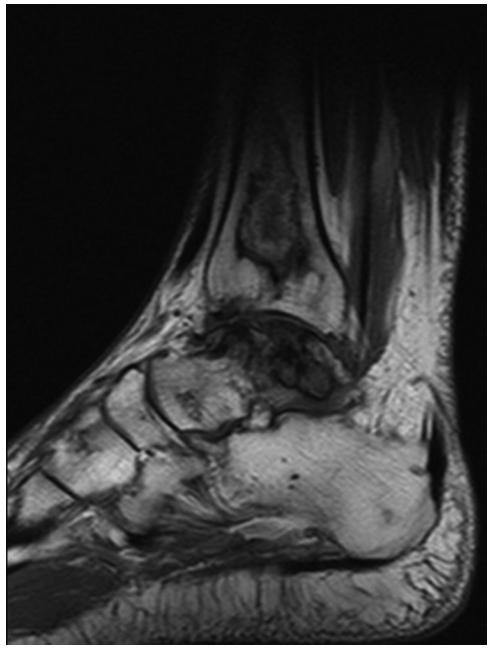

FIGURE 3. Sagittal MRI demonstrating serpentine areas of bone infarcts in the distal tibia and talus and ON of cuneiform bone.

prothrombotic tendency, or merely a secondary reactive phenomenon.[51] However, very elevated levels of factor VIII over a relatively long time are suggestive of a factor VIII elevation independent of inflammation.[35] In addition, there is consistent evidence that the elevation of factor VIII may not be an acute post-thrombotic phenomenon. Several studies have demonstrated that this factor remains elevated several months and even years after the thrombotic event.[28,32,33,47] Moreover, a 2011 prospective study in patients with DVT[57] demonstrated that factor VIII levels are partially influenced by the acute phase reaction, but remain elevated during follow-up, despite treatment with oral anticoagulants. Other studies have also demonstrated that the elevation of factor VIII is independent from elevations of other acute phase reactants, such as C-reactive protein or fibrinogen.[46]

In the current study, aPL positivity was the second most common prothrombotic alteration. It was more frequently observed in patients with multifocal ON (20% presenting with aPL), compared with 6% of patients with DVT and none of the control patients. Additionally, 3 of our patients fulfilled criteria for primary APS.[40] Although the frequency of ON in primary APS seems to be low, it is probably an underestimated clinical complication. Of the different reported cohorts of patients with primary APS, to our knowledge only 2 have reported associated cases of ON: Asherson et al[3] described 2 (3%) cases out of 70 patients, and in the "Euro-phospholipid" cohort,[8] 2.4% of the 1000 patients had associated ON, with none of the other series of primary APS[13,16,23,38,60] describing other cases of ON. The association between primary APS and ON is derived from isolated case reports[25] and, especially, from a single controlled study of 75 APS patients.[56] This study prospectively evaluated the prevalence of ON in asymptomatic APS patients by MRI of the femoral heads. The study included 30 patients with primary APS, 19 patients with SLE who were not previously treated with corticosteroids (10 negative for aCL and 9 with aCL but not APS), and 30 healthy subjects. It is noteworthy that asymptomatic ON was revealed in 20% of the patients with

TABLE 6. Patients With Multifocal ON, Previous and Present Studies

Source First Author (Ref)	No. of Patients	Mean Age (yr)	Mean Bone Lesions per Patient	Cause	Coagulation Abnormalities
Laporte[34]	32	34	6.3	Most patients had related systemic diseases (SLE, inflammatory bowel disease, renal transplant)	One patient with protein S deficiency and 1 with high tissue plasminogen inhibitor
Glueck[18]	26	48 (Idiopathic), 44 (Secondary)	5.4 (Idiopathic), 5 (Secondary)	13 Idiopathic, 13 Secondary	Higher levels of factor VIII, lower levels of free protein-S, and higher prevalence of homocystinemia
Mont[42]	19	39*	3.3†	NR	ND
Flouzat-Lachaniete[14]	87	26	5.2	Sickle cell disease	ND
Anonymous (Collaborative Osteonecrosis Group)[2]	101	36	6.2	Most patients had related systemic diseases (SLE, renal disease, inflammatory bowel disease)	Twelve (86%) 14 patients tested were found to have a coagulation disorder
Jones[27]	8	46‡	NR	5 Idiopathic	Elevated PAI-Fx was the most frequent abnormality noted (n = 4)
				40 Secondary‡	
Present report	29	49	5.2	4 Idiopathic 25 Secondary	Coagulation abnormalities in 48% of patients (mainly high levels of factor VIII and aPL)

Abbreviations: See previous tables.
*Mean age of the total number of patients with ON (n = 48, 19 with multifocal ON).
†Bone lesions of the total number of patients with ON.
‡Mean age and causes from the total number of patients with ON (n = 45, 8 with multifocal ON).

primary APS, whereas none of the SLE patients or control patients had positive MRI findings for ON, thereby suggesting that ON represents a common feature of primary APS that can be detected by MRI in its early stages.

APS patients may also present with ON at atypical sites, such as the vertebral body or the lunate bone (Kienböck disease),[1] occasionally being the only clinical manifestation of APS. Additionally, multifocal ON has been described in association with catastrophic APS.[11] To date, 5 cases with ON of a total of 282 patients collected from the catastrophic APS Registry have been described (http://infmed.fcrb.es/es/web/caps).

The risk of thrombosis in aPL-positive carriers is difficult to estimate accurately because of the multifactorial nature of thrombosis. Currently, it is well known that patients with triple positivity for aPL (LA, aCL, and anti-β2-glycoprotein I) are considered to have a higher risk for thrombosis.[49] In fact, these patients may develop recurrent thrombotic episodes, despite the use of oral anticoagulants.

The effectiveness of aspirin in aPL-positive carriers without previous thrombosis is not fully supported by the current literature: in a randomized, double-blind, placebo-controlled trial, low-dose aspirin (81 mg daily) seemed to be no better than placebo in preventing first thrombotic episodes in asymptomatic, persistently aPL-positive patients.[12] Nonetheless, based on its low cost and toxicity, prophylactic treatment with aspirin seems to be a easonable option in asymptomatic patients persistently positive for aPL.[58]

Based on current recommendations for the treatment of APS patients, at present there is no clear indication for anticoagulation in patients with ON as the only thrombotic manifestation of the disease.[58] The best approach might be antiaggregation (low dose of aspirin) with strict control of other thrombotic risk factors. In patients with multifocal ON or with the onset of new ON in other territories, oral anticoagulation could be a good, albeit not yet proven, option.[25] Four APS patients in the current series received anticoagulation therapy, and 2 of them had additional ON episodes. One patient with associated aCL had antiaggregation treatment and did not have any new ON episodes.

Seven of 29 patients in the current series had HIV infection. These patients are at a substantially increased risk for the development of ON, occurring not infrequently in the form of multifocal ON and early in the course of the disease. In HIV patients, the main risk factors for the development of ON include the HIV infection per se; corticosteroid use; antiretroviral therapy, especially protease inhibitors; and aPL.[45] In a recent case-control study, a CD4 cell count <60 cells/μL and corticosteroid use were the main factors associated with the increased risk for ON. No specific thrombophilia tests were significantly associated with ON.[10] Nevertheless, in an earlier study, Miller et al[39] observed MRI findings consistent with ON of the femoral head in 4.4% of a group of 339 HIV-infected patients, with 93% of these patients having aCL (half with antibody levels >23 IgG phospholipid units). In a subsequent study by the same group,[43] 239 of 339 original participants underwent a second MRI screening, with a mean follow-up period of 23 months after the initial MRI (range, 17–31 mo). The incidence of hip ON was 0.65 cases per 100 patient-years, showing a 100-fold elevated risk of ON in HIV-infected patients compared with the general population.[41] Other series have also confirmed the presence of prothrombotic abnormalities in HIV individuals, especially the presence of aCL observed in 77% and anti-protein S antibodies in 28% of the patients, respectively.[53] Four of the 7 HIV-infected patients in the current series had prothrombotic abnormalities; elevated factor VIII and the presence of aCL were the most frequent.

Finally, a paradoxic case in the current study involved a 34-year-old man with a previous history of spontaneous hemorrhage (subdural hematoma) with low platelet aggregation tests, including acid arachidonic and adenosine diphosphate, and no other known risk factors related to the development of ON. To our knowledge, low platelet aggregation has not previously been related to ON. Conversely, as expected, animal studies have demonstrated that the use of antiplatelet drugs, such as clopidogrel, prevented the development of corticosteroid-induced ON.[61] The pathogenesis of ON in this particular case remains unclear.

The current study has certain strengths and limitations. It could be argued that we have included a relatively low number of patients. Nevertheless, taking the low prevalence of this process into account, this study describes one of the largest cohorts of multifocal ON from a single center to date. Although the specific role of the observed coagulation abnormalities in the development of ON is not known, considering the previous history of corticosteroid use in most of the patients, it seems logical to assume these abnormalities are a contributory factor. Indeed, patients with associated coagulation abnormalities also had a higher number of ON-affected bones.

In conclusion, in the current study most patients with multifocal ON had secondary conditions that may be associated with the development of ON, such as steroid treatment or HIV infection. However, more than half of these patients also had prothrombotic-associated factors, especially high levels of factor VIII and aPL, which can contribute to the development of multifocal ON. The current findings may have major implications for the diagnosis and treatment of this condition, and clearly indicate that a thrombophilic profile must be performed in these patients.

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