Chapter 1
Osteonecrosis and Thrombophilia: Pathophysiology, Diagnosis, and Treatment

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Case Presentation 1

This previously healthy 47-year-old female was started on an estrogen-testosterone patch to improve libido that was followed by the onset of intermittent right hip pain. When seen by us 2 years later, her pain had increased to the point that she could walk only short distances with a cane.

Diagnosis/Assessment

X-ray of the hips was normal, but MRI revealed Ficat stage I osteonecrosis of the right hip. There was no history of big-dose long-term steroids, alcoholism, or any other causes

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for secondary osteonecrosis [1]. We carried out our usual diagnostic panel of laboratory tests of thrombophilia and hypofibrinolysis (Table 1.1). Studies of thrombophilia-hypofibrinolysis revealed previously undiagnosed heterozygosity for the prothrombin G20210A mutation, a thrombophilic, autosomal dominant mutation, associated with increased risk of venous thrombosis [2] and osteonecrosis [3]. All other coagulation tests, as displayed in Table 1.1, were negative. We believe that the osteonecrosis of the hip was caused by an interaction of the exogenous estrogen-testosterone and the thrombophilic prothrombin gene mutation [4].

Sonography of leg veins revealed no signs of deep venous thrombosis.

Management

The estrogen-testosterone patch was immediately discontinued**.** In the absence of contraindications to anticoagulation, enoxaparin 1.5 mg/kg/day in two divided doses was started. After completion of a 3-month course of enoxaparin, standard in our initial study protocol as required by the FDA [5], ambulation was pain-free. After being asymptomatic for an additional 8 months, right hip pain returned, and enoxaparin was restarted. After 3 months on the second course of enoxaparin, she again became asymptomatic. A repeat MRI revealed Ficat stage I osteonecrosis, without change from the pretreatment study.

Xarelto, 10 mg/day, was then started. She remained asymptomatic for the subsequent 9 months. Repeat MRI revealed no change, still Ficat stage I osteonecrosis.

Outcome

She remains entirely asymptomatic 3 years after initial diagnosis, being maintained on Xarelto 10 mg/day. In patients with major gene thrombophilias and Ficat stages I–II osteonecrosis at the time of first beginning anticoagulation, progression

TABLE 1.1 Coagulation disorders in patients with idiopathic and secondary osteonecrosis

	Factor V Leiden	**PTG TC**	**PAIG 4G4G**	**MTHFR TT**	**Factor VIII >150%**	**Factor XI >150%**	**Homocysteine high[a]**
Idiopathic osteonecrosis	20/220	10/213	59/210	44/211	39/161	10/154	24/196
(n = 221)	(9%)	(5%)	(28%)	(21%)	(24%)	(6%)	(12%)
Normal control	2/109	3/107	26/104	32/109	7/103	3/101	5/107
(n = 110)	(2%)	(3%)	(25%)	(29%)	(7%)	(3%)	(5%)
Idiopathic vs controls Fisher's p	*.017*	NS	NS	NS	*.0002*	NS	*.04*
Secondary osteonecrosis	9/111	3/109	31/109	32/110	10/69	3/61	17/108
(n = 113)	(8%)	(3%)	(28%)	(29%)	(14%)	(5%)	(16%)
Normal control	2/109	3/107	26/104	32/109	7/103	3/101	5/107
(n = 110)	(2%)	(3%)	(25%)	(29%)	(7%)	(3%)	(5%)
Secondary vs controls Fisher's p	.059	NS	NS	NS	NS	NS	*.012*

(continued)

Table 1.1 (continued)

	ACLA IgG high[b]	ACLA IgM high[c]	Antigenic Protein C <73%	Antigenic Protein S <63%	Antigenic Free S <66%	Antithrombin III <80%	Lupus positive
Idiopathic osteonecrosis	11/194	22/193	9/190	1/192	8/173	7/188	2/188
(n = 221)	(6%)	(11%)	(5%)	(0.5%)	(5%)	(4%)	(1%)
Normal control	6/109	2/109	6/96	4/96	2/96	2/96	2/110
(n = 110)	(6%)	(2%)	(6%)	(4%)	(2%)	(2%)	(2%)
Idiopathic vs controls Fisher's p	NS	*.003*	NS	*.04*	NS	NS	NS
Secondary osteonecrosis	5/106	10/106	3/100	3/99	16/95	2/97	5/101
(n = 113)	(5%)	(9%)	(3%)	(3%)	(17%)	(2%)	(5%)
Normal control	6/109	2/109	6/96	4/96	2/96	2/96	2/110

(n = 110)	(6%)	(2%)	(6%)	(4%)	(2%)	(2%)	(2%)
Secondary vs controls Fisher's p	NS	*.018*	NS	NS	*.0004*	NS	NS

PTG prothrombin G20210A mutation, *PAIG* PAI-1 4G/5G promoter polymorphism, *MTHFR* methylenetetrahydrofolate reductase C677T/A1298C, *Free S* protein S free, *TT* homozygous mutant, *TC* heterozygote mutant, *CC* wild type normal

[a]Dated cut point for Homocysteine high: *≥13.5 umol/l (before 3/20/2005); ≥12 (3/21/05–3/27/06); ≥10.4 (3/28/06–4/14/08); ≥11.4 (4/15/08–11/14/08); ≥15 (after 11/15/08)(6/9/15 revised)*

[b]Dated cut point for IgG high: *≥23 GPL (before 10/31/12); ≥15 (after 11/1/12)*

[c]Dated cut point for IgM high: ≥10 MPL (before 4/30/12); ≥13 (after 5/1/12)

to joint collapse can usually be prevented, pain ameliorated, and function maintained [6]. Long-term anticoagulation also carries increased bleeding risk, but this is much less with the new Xa inhibitors than Coumadin [7–9].

Case Presentation 2

In January 2008, this 54-year-old Caucasian male developed increasing fatigue and loss of libido. Workup revealed low testosterone levels. A diagnosis of hypogonadism was made. He was then started on a testosterone patch (50 mg/ day) in February 2008. Six months after starting the testosterone patch**,** he developed severe bilateral hip pain. X-rays revealed bilateral osteonecrosis of the hips, right hip Ficat stage II and left Ficat stage I. On our evaluation of thrombophilia-hypofibrinolysis (Table 1.1), he was found to be heterozygous for the factor V Leiden mutation and homozygous for the MTHFR C677T mutation (associated with abnormal homocysteine metabolism). There were no risk factors for secondary osteonecrosis, and we attributed the development of the osteonecrosis to an interaction between the thrombophilic factor V Leiden mutation and exogenous testosterone therapy [4, 10].

Management

Testosterone was stopped. Enoxaparin, 1.5 mg/kg/day in two divided doses, was started and maintained for 3 months as usual. Four months later, MRI and X-ray showed no change from pretreatment, but his pain was much less. Because of persistent pain, a second 3-month course of enoxaparin was given, and he became asymptomatic. Eight months later, there was no change in his X-ray or MRI. Three years from initial treatment with enoxaparin, MRIs were unchanged. There were no new areas of osteonecrosis or marrow edema compared to pretreatment. Because of symptomatic improvement on enoxaparin and stable X-rays and magnetic resonance

images (MRIs), chronic long-term anticoagulation was started 3 years after diagnosis with Pradaxa 150 mg twice per day.

Outcome

Five years after initial diagnosis, still on Pradaxa**,** no radiographic features of ON were identified in either hip. Nine years after diagnosis, still on Pradaxa, he remains asymptomatic, with no radiographic features of ON identified.

Case Presentation 3

This African-American female was originally seen at age 69 with severe left hip pain and moderately severe right hip pain. At pretreatment entry, X-rays revealed that the left hip was collapsed (Ficat stage III), but the right hip was Ficat II (Fig. 1.1). Coagulation tests

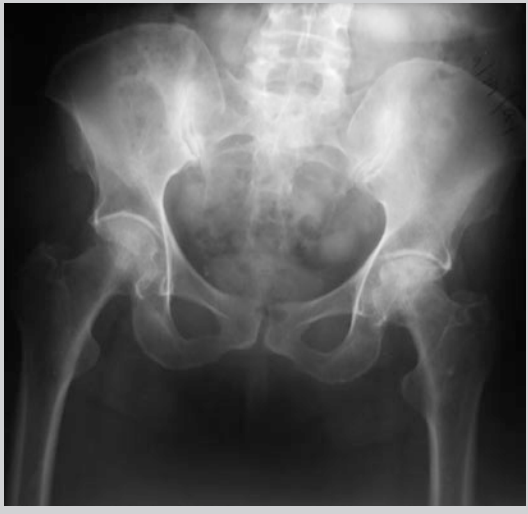

FIGURE 1.1 Pretreatment hip X-ray, Case #3. *Left* hip collapsed (Ficat stage (III), *right* hip Ficat stage II

revealed resistance to activated protein C, but PCR revealed wild-type normal factor V without the Leiden mutation. In such cases, there is usually a different mutation in the factor V gene (factor V Cambridge) [11], but the clinical thrombophilia is the same as if there were factor V Leiden heterozygosity.

Management

Because of financial constraints, anticoagulation was started with Coumadin rather than the usual enoxaparin. After 16 months on Coumadin, the right hip was asymptomatic and was unchanged on X-ray examination (Fig. 1.2). Total hip replacement was done on the left, as expected with Ficat III classification at presentation. In all of our studies

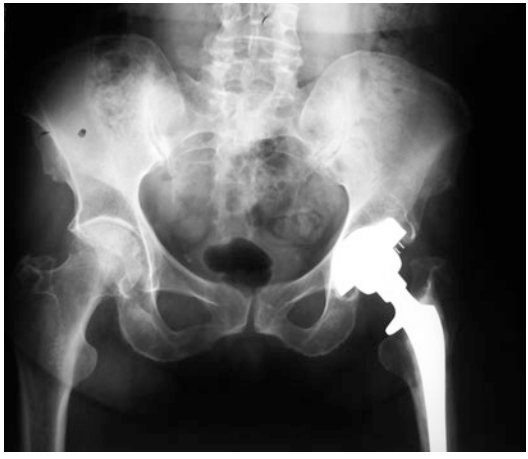

Figure 1.2 Hip X-ray after 16 months on Coumadin. *Right* hip Ficat stage II, unchanged from pretreatment. Total hip replacement had been done on the Ficat stage III *left* hip

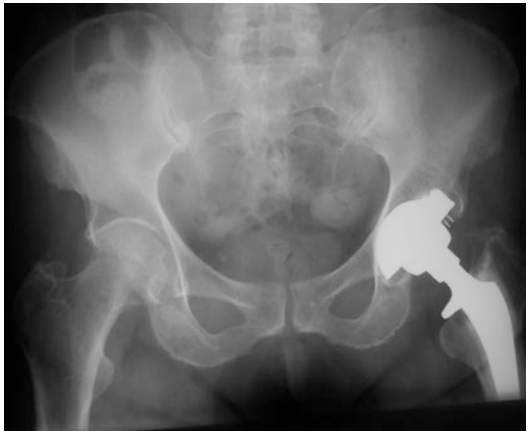

FIGURE 1.3 Hip X-ray after 13 years on Coumadin. *Right* hip Ficat stage II, unchanged from pretreatment

of anticoagulation in patients with idiopathic osteonecrosis with one hip or knee Ficat stage I or II compared to patients with stage III or IV, almost all the Ficat stage I–II joints were protected by anticoagulant treatment and did not manifest progression, but the stage III–IV joints progressed despite anticoagulation, usually requiring total joint replacement [5, 6, 12, 13]. After 13 years on Coumadin, the right hip remained asymptomatic, and the X-ray was unchanged (Ficat stage II) (Fig. 1.3).

Outcome

Within 16 months on Coumadin, the right hip became symptom-free and remained symptom-free for 11.5 subsequent years, for a total of 13 years on anticoagulation. In patients whose idiopathic Ficat stages I or II osteonecrosis are associated with familial thrombophilia, the average time

from the initiation of anticoagulation to becoming symptom-free is 7 months [6].

Literature Review

When evaluating patients with osteonecrosis, particularly multifocal, physicians should first differentiate between osteonecrosis secondary to high-dose long-term corticosteroids, alcoholism, fracture dislocation, etc., and primary ("idiopathic") osteonecrosis. We believe that thrombophilia, hypofibrinolysis [13–16], and eNOS-mediated abnormalities of nitric oxide metabolism [17, 18] play important roles in the pathogenesis of idiopathic osteonecrosis.

We have noted that when compared to normal controls, consecutively referred patients with idiopathic osteonecrosis are more likely to have familial thrombophilia including heterozygosity for the factor V Leiden mutation, high factor VIII, high homocysteine, and high anticardiolipin antibody IgM (Table 1.1).

Patients with osteonecrosis secondary to steroids, alcohol excess, trauma, etc., are marginally more likely ($p = .059$) than normal controls to have factor V Leiden heterozygosity, as well as high homocysteine, anticardiolipin antibody IgM, and low antigenic free protein S (Table 1.1).

The natural history of untreated, idiopathic osteonecrosis of the hip is 20–50 % hip survival within a 2-year follow-up period [19]. Mont et al. [20] concluded "…while small medially located lesions have a low rate of progression, the natural history of asymptomatic, medium-sized, and especially large, osteonecrotic lesions is progression in a substantial number of patients." In subjects with idiopathic osteonecrosis and familial thrombophilia-hypofibrinolysis, provided that anticoagulant therapy is started before segmental collapse of the involved bone (Ficat stages I or II), osteonecrosis may be arrested or even reversed [5, 12, 13]. There were 6200 total hip replacements in the USA for osteonecrosis in 2008 [21]. Diagnosis of medically treatable etiologies of osteonecrosis

before bone collapse has been shown to reduce the incidence of total hip and knee replacement [5, 6, 12, 22].

The pathogenesis of osteonecrosis (ON) probably reflects a "multiple etiology" [23] model. We [13], and then others [14], have postulated a sequence for development of ON: venous thrombosis due to thrombophilia-hypofibrinolysis causes osseous venous outflow obstruction, leading to increased intraosseous venous pressure, reduced arterial flow, ischemia, and bone death. Experimental models of ON [24] confirm venous occlusion as the primary event.

Primary (idiopathic) ON of hips and knees [25] in adults [3] and Legg-Calve-Perthes (LCP) in children [26, 27] is commonly associated with thrombophilia-hypofibrinolysis. Factor V Leiden heterozygosity and high anticardiolipin antibody (ACLA) IgG and IgM are associated with LCP in childhood [26]. In adults, relationships have been described between ON and factor V Leiden heterozygosity [28], hypofibrinolysis [18], or reduction of nitric oxide (NO) production by the T-786C mutation of the endothelial nitric oxide synthase gene (eNOS) [18].

The association of heritable thrombophilia-hypofibrinolysis with ON is important because the diagnosis provides a medical (anticoagulation) approach to decrease the frequency of total

Clinical Pearls and Pitfalls

- In the presence of major gene thrombophilia [6, 12, 13], particularly factor V Leiden or prothrombin gene heterozygosity, exogenous estrogen or (particularly) testosterone appears to interact with the heritable thrombophilia, leading to deep venous thrombosis, pulmonary embolus, and osteonecrosis [4, 10].
- In cases with otherwise idiopathic osteonecrosis of the hip or knee, provided that the exogenous estrogen-testosterone is discontinued and anticoagulation is initiated, usually medical treatment can relieve the pain, allowing normal physical activity, possibly with slow healing of the osteonecrotic bone.

- Familial thrombophilia (factor V Leiden heterozygosity) and hypofibrinolysis (4G4G PAI-1 gene homozygosity) can be associated with multifocal idiopathic osteonecrosis but more commonly with unifocal osteonecrosis (Table 1.1).
- Particularly in the presence of factor V Leiden heterozygosity [6, 12, 13], provided that anticoagulation is started before structural collapse of the bone (Ficat stages I–II), idiopathic osteonecrosis can be stabilized, with resolution of pain and resumption of normal function. Long-term (4–16 years) anticoagulation, initiated in Ficat stages I–II of idiopathic hip osteonecrosis patients with familial thrombophilia, can change the natural history of osteonecrosis, stopping progression, resolving pain, and restoring function [6].
- Because there is also a definite association between coagulation disorders and secondary osteonecrosis (Table 1.1), the patient's history is very important, since anticoagulation initiated in Ficat stages I–II of secondary osteonecrosis does not appear to alter the course of the disease [5].
- In those patients with Ficat stages III and IV osteonecrosis, although anticoagulation cannot forestall the need for total joint replacement, presurgical determination of thrombophilia-hypofibrinolysis identifies patients at high risk for postoperative deep venous thrombosis-pulmonary embolism for whom vigorous postoperative thromboprophylaxis would be particularly important [29–32].
- In patients hetero-or homozygous for the T786C eNOS mutation, addition of 9 g/day of over the counter L-Arginine [33] may slow progression of osteonecrosis [34].

hip replacement (THR) and total knee replacement [6, 12, 13]. We speculate that enoxaparin can stop the progression of Ficat stages I and II primary ON of the femoral head by facilitating lysis of intraosseous thrombi, allowing bone healing [5, 6].

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