

Case Report

Avascular Necrosis of Bone following Chemotherapy in Cancer Patients with Coagulopathy: Report of Two Cases

Hui-Ching Hsu^a Tzu-Yao Liao^b Dave Wei-Chih Chen^c Yu-Hsiang Juan^d
Chuang-Chi Liaw^b

^aDivision of Chinese Acupuncture and Traumatology, Department of Traditional Chinese Medicine, Chang-Gung Memorial Hospital and Chang-Gung University College of Medicine, Taoyuan, Taiwan; ^bDivision of Hemato-Oncology, Department of Internal Medicine, Chang-Gung Memorial Hospital and Chang-Gung University College of Medicine, Taoyuan, Taiwan; ^cDepartment of Orthopedic Surgery, Chang-Gung Memorial Hospital and Chang-Gung University College of Medicine, Taoyuan, Taiwan; ^dDepartment of Medical Imaging and Intervention, Chang-Gung Memorial Hospital and Chang-Gung University College of Medicine, Taoyuan, Taiwan

Keywords

Avascular necrosis of bone · Solid tumor · Chemotherapy · Coagulopathy · Low-molecular-weight heparin · Bipolar arthroplasty

Abstract

We report 2 cases of patients with solid tumors and coagulopathy who experienced avascular necrosis (AVN) of the bone following chemotherapy. Both cases exhibited nontraumatic bilateral AVN of the femoral heads, and one also showed bilateral AVN of the humeral heads. One case had multiple thromboembolic complications, including pulmonary obstructive syndrome and paraneoplastic pain. The other showed multiple paraneoplastic syndromes, with hypercalcemia and thrombocytosis. Groin pain and claudication of the lower extremities developed and persisted. Both patients eventually received bilateral hip arthroplasty due to AVN of both femoral heads.

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Published by S. Karger AG, Basel

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Chuang-Chi Liaw, MD
Division of Hemato-Oncology, Department of Internal Medicine
Chang-Gung Memorial Hospital, 5, Fusing St., Gueishan Township
Taoyuan City 333 (Taiwan)
E-Mail e102309@adm.cgmh.org.tw

Introduction

Avascular necrosis (AVN) of the femoral head is a pathological process that results from disruption of the blood supply to the bone and occurs most commonly in the femoral epiphysis [1]. Patients usually present with pain and limited joint motion [1]. The risk factors are not completely understood [2, 3]. Nontraumatic necrosis of the femoral head was also mentioned [4, 5]. The mechanism involves impaired circulation to a specific area that ultimately becomes necrotic. Furthermore, coagulation disorders have been reported in patients with AVN of the femoral head [6]. AVN is most frequently associated with high doses of oral and intravenous corticosteroids and prolonged duration of therapy [7]. Cancer patients receiving chemotherapy are usually also treated with corticosteroids for the prophylaxis of emesis [8]. AVN of the humeral head has rarely been reported [9], although one case of bilateral AVN of the humeral heads has been reported in a patient with Hodgkin lymphoma following therapy [10].

We report 2 cases of cancer patients with coagulopathy following chemotherapy. The first was a patient with breast cancer and bilateral AVN of the femoral and humeral heads. The second was a patient with malignant thymoma and bilateral AVN of the femoral heads.

Case Reports

Case 1

Case 1 was a 54-year-old woman with recurrent bilateral breast cancer, who was hospitalized in July 2009 with dyspnea. Her chest X-rays showed no abnormalities, but the chest computed tomography (CT) scan showed a tumor or thrombus over the right pulmonary vein and entering the left atrium (Fig. 1a). The D-dimer value was 518 ng/mL (normal range <500 ng/dL). The patient received chemotherapy with 5-fluorouracil, leucovorin, vinorelbine, and cisplatin every 4 weeks, as well as daily subcutaneous treatment with a low-molecular-weight heparin (LMWH), Fraxiparine (GlaxoSmithKline). The dyspnea improved during the chemotherapy course, but migrating pain, paraneoplastic pain, and swelling occurred over the left infra-auricular area. Dexamethasone was given for the prophylaxis of emesis and to improve the coagulation disorder.

The patient complained of pain and numbness localized to the bilateral groin area, especially the left side, and from July 2012 had difficulty walking. The pelvis X-ray showed bilateral AVN of the femoral heads (Fig. 1b). Bipolar hip arthroplasty was performed on the left hip in September 2012 and on the right hip in November 2012. The CT scan showed osteonecrosis of the right femoral head after bipolar surgery had been performed on the left femoral head (Fig. 1c). Pathological specimens of both femoral heads showed AVN, but no cancer cells were seen.

The patient also complained of bilateral shoulder pain, especially on the left side. The plain X-ray showed osteonecrosis of both the humeral heads (Fig. 2a, b). The chest CT scan revealed bilateral osteonecrosis of the humeral heads, which was more severe on the left side (Fig. 2c).

The patient received a total of 40 courses of chemotherapy. She complained of severe left chest pain from October 2014, and we suspected acute coronary syndrome related to cancer with coagulopathy. The chest X-ray revealed cardiomegaly, and echocardiography showed a large quantity of pericardial effusion. The patient died of tumor progression and brain death in November 2014.

Case 2

Case 2 was a 51-year-old man with malignant thymoma, who was hospitalized in 2012 with dyspnea. He also exhibited paraneoplastic syndromes with hypercalcemia (serum calcium 12.4 mg/dL, normal range 7.9–9.9 mg/dL) and thrombocytosis (platelet count $824 \times 10^3/\mu\text{L}$, normal range $50\text{--}450 \times 10^3/\mu\text{L}$). His D-dimer value was $>10,000$ ng/mL (normal range <500 ng/dL). The chest X-ray and CT scan revealed a large anterior mediastinal mass (Fig. 3a). The patient received chemotherapy with 5-fluorouracil, leucovorin, and cisplatin every 4 weeks as well as daily subcutaneous treatment with an LMWH, enoxaparin (Sanofi-Aventis). Dexamethasone was given for the prophylaxis of emesis.

The anterior mediastinal mass decreased in size following chemotherapy. The subsequent CT scan revealed this decrease as well as a tumor or thrombus over the right pulmonary vein and left atrium (Fig. 3b). The patient received regular chemotherapy but refused radiotherapy. An initial tumor response was noted; however, later this lesion progressed.

The patient complained of pain localized to the groin area and difficulty in walking in November 2012. The pelvis X-ray revealed bilateral AVN of the femoral heads (Fig. 3c). Bipolar hip arthroplasty was performed on the left hip in January 2013 and on the right hip in April 2013. Pathological specimens of both femoral heads showed AVN, but no cancer cells were seen. The patient received a total of 10 courses of chemotherapy, but died of tumor progression and respiratory failure in February 2014.

Discussion

These 2 cases experienced nontraumatic bilateral AVN of the femoral heads, and one also had bilateral humeral head AVN. Both received chemotherapy and exhibited coagulopathy with a tumor or thrombus over the right pulmonary vein and left atrium. One also had multiple thromboembolic complications, including pulmonary obstructive syndrome [11] and paraneoplastic pain [12]. The other showed multiple paraneoplastic syndromes, including hypercalcemia and thrombocytosis.

The disruption of the blood supply to the hip and shoulder was due to arterial insufficiency in these areas, probably caused by paradoxical embolism [13, 14]. Paradoxical embolism is defined as the passage of a clot (thrombus) from a vein to an artery [11]. A tumor or thrombus was observed in the right pulmonary vein and left atrium in both cases. When a clot in a vein breaks off, it can lodge in an artery, causing localized ischemia. This can occur in the limbs, causing resting pain, as well as in the brain, causing a cerebral infarction [13, 14]. Claudication is defined as the pain caused by insufficient blood flow to an area, usually during exercise. This condition generally affects the legs, but can also affect the arms [15].

Thrombosis in arteries has long been recognized in cancer patients, although the exact mechanisms remain obscure [16]. A potential mechanism may be endothelial damage in the arterial wall, causing the loss of the blood's natural anticoagulant properties [16, 17]. Virchow described three factors (venous stasis, endothelial injury, and hypercoagulability) that are thought to contribute to venous and arterial thrombosis [16]. The mechanism of the prothrombotic state is complex in cancer patients: cancer cells can activate the hemostatic system via the expression of adhesion molecules, the release of inflammatory cytokines, and the production of hemostatic factors [18]. Cytokine production is intricately related to both tumor production and the patient's reaction to factors such as infection, chemotherapy, and invasive therapeutic procedures [19].

Both patients in this case study experienced multiple courses of chemotherapy, resulting in increased production of cytokines, which caused the formation of thrombi and decreased arterial blood supply. Blood disruption to the epiphyses of the femoral and humeral heads led to the development of AVN. The first case exhibited multiple thromboembolic complications, including pulmonary obstructive syndrome, dyspnea [11], and paraneoplastic migratory pain [12]. These cases were unusual, since AVN usually occurs in patients with hematological malignancies [20–22] and is rarely seen in cases with solid tumors [23].

After detection of the tumor or thrombus in the pulmonary vein and left atrium, both patients received regular scheduled chemotherapy, as well as continuous LMWH at the beginning of the chemotherapy course. The first case also received prolonged dexamethasone and intravenous fluid therapy in order to decrease cytokine production, because of multiple episodes of thromboembolic complications. There has been no benefit reported from using LMWH or oral anticoagulant treatment for intermittent claudication [24]. Both patients eventually received bilateral hip arthroplasty due to AVN of both femoral heads [25], and both died of cancer with coagulopathy: one from brain death and the other from respiratory failure.

Conclusion

Cancer patients with coagulopathy undergo chemotherapy and anticoagulant therapy. When they complain of groin pain and claudication, AVN of the femoral head should be the differential diagnosis.

Statements of Ethics

The study was approved by the Chang Gung Medical Foundation.
Institutional Review Board IRB No.: 201701703B0.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was given for this case report.

References

- 1 Kerachian MA, Harvey EJ, Cournoyer D, Chow TY, Séguin C. Avascular necrosis of the femoral head: vascular hypotheses. *Endothelium*. 2006 Jul-Aug;13(4):237–44.
- 2 Shah KN, Racine J, Jones LC, Aaron RK. Pathophysiology and risk factors for osteonecrosis. *Curr Rev Musculoskelet Med*. 2015 Sep;8(3):201–9.
- 3 Tsai SW, Wu PK, Chen CF, Chiang CC, Huang CK, Chen TH et al. Etiologies and outcome of osteonecrosis of the femoral head: etiology and outcome study in a Taiwan population. *J Chin Med Assoc*. 2016 Jan;79(1):39–45.

- 4 Mont MA, Cherian JJ, Sierra RJ, Jones LC, Lieberman JR. Nontraumatic Osteonecrosis of the Femoral Head: Where Do We Stand Today? A Ten-Year Update. *J Bone Joint Surg Am*. 2015 Oct;97(19):1604–27.
- 5 Etienne G, Mont MA, Ragland PS. The diagnosis and treatment of nontraumatic osteonecrosis of the femoral head. *Instr Course Lect*. 2004;53:67–85.
- 6 Garcia FL, Ramalli EL, Picado CH. Coagulation disorders in patients with femoral head osteonecrosis. *Acta Orthop Bras*. 2013 Jan;21(1):43–5.
- 7 Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open Orthop J*. 2012;6:449–57.
- 8 Barbour SY. Corticosteroids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Canc Netw*. 2012 Apr;10(4):493–9.
- 9 Harreld KL, Marker DR, Wiesler ER, Shafiq B, Mont MA. Osteonecrosis of the humeral head. *J Am Acad Orthop Surg*. 2009 Jun;17(6):345–55.
- 10 Virgolini L, De Maglio A. Bilateral aseptic necrosis of the humeral head following combined therapy for Hodgkin's lymphoma. *Ital J Orthop Traumatol*. 1992;18(4):543–6.
- 11 Liaw CC, Chang H, Yang TS, Wen MS. Pulmonary venous obstruction in cancer patients. *J Oncol*. 2015;2015:210916.
- 12 Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F. Management of cancer pain: ESMO clinical recommendations. *Ann Oncol*. 2012 Oct;23 Suppl 7:vii39–154.
- 13 Windecker S, Stortecky S, Meier B. Paradoxical embolism. *J Am Coll Cardiol*. 2014 Jul;64(4):403–15.
- 14 Travis JA, Fuller SB, Ligush J Jr, Plonk GW Jr, Geary RL, Hansen KJ. Diagnosis and treatment of paradoxical embolus. *J Vasc Surg*. 2001 Nov;34(5):860–5.
- 15 Schainfeld RM. Management of peripheral arterial disease and intermittent claudication. *J Am Board Fam Pract*. 2001 Nov-Dec;14(6):443–50.
- 16 Blann AD, Dunmore S. Arterial and venous thrombosis in cancer patients. *Cardiol Res Pract*. 2011 Mar;2011:394740.
- 17 Ross JS, Stagliano NE, Donovan MJ, Breitbart RE, Ginsburg GS. Atherosclerosis: a cancer of the blood vessels? *Am J Clin Pathol*. 2001 Dec;116 Suppl:S97–107.
- 18 Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol*. 2008 Oct;143(2):180–90.
- 19 Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost*. 2013 Feb;11(2):223–33.
- 20 Hui L, Wiernik PH. Avascular necrosis of bone after adult acute lymphocytic leukemia treatment with methotrexate, vincristine, L-asparaginase, and dexamethasone (MOAD). *Am J Hematol*. 1996 Jul;52(3):184–8.
- 21 Abhyankar D, Nair R, Menon H, Kapoor B, Advani S. Avascular necrosis of head of femur in a patient with acute promyelocytic leukemia. *Leuk Lymphoma*. 2000 May;37(5–6):635–7.
- 22 Sakakura M, Nishii K, Usui E, Monma F, Tsukada T, Shiku H. Bilateral osteonecrosis of the head of the femur during treatment with retinoic acid in a young patient with acute promyelocytic leukemia. *Int J Hematol*. 2006 Apr;83(3):252–3.
- 23 van den Berkmortel F, de Wit R, de Rooy J, DeMulder P. Osteonecrosis in patients with testicular tumours treated with chemotherapy. *Neth J Med*. 2004 Jan;62(1):23–7.
- 24 Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev*. 2014 May;7(5):CD001999.
- 25 Roth A, Beckmann J, Bohndorf K, Fischer A, Heiß C, Kenn W et al. S3-Guideline non-traumatic adult femoral head necrosis. *Arch Orthop Trauma Surg*. 2016 Feb;136(2):165–74.



Fig. 1. Case 1 was a 54-year-old female with breast cancer who was receiving chemotherapy. **a** The chest CT scan (axial view) showed a tumor or thrombus (arrowhead) over the right posterior proximal pulmonary vein and entering the left atrium. **b** The plain X-ray revealed bilateral osteonecrosis of the femoral heads (arrows). **c** The pelvis CT scan (axial view) showed osteonecrosis of the right femoral head (arrow) after arthroplasty of the left hip joint.

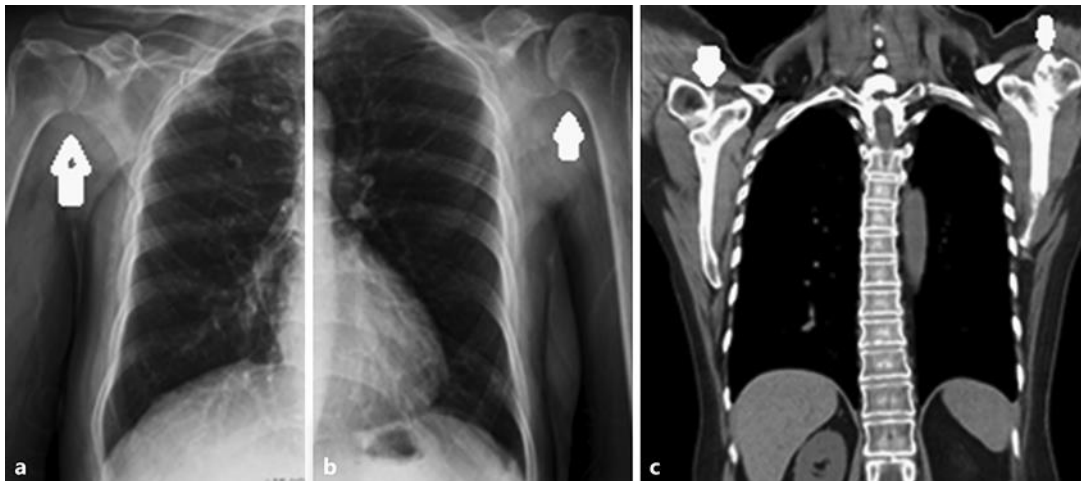


Fig. 2. Shoulder lesions of case 1. The plain X-ray revealed osteonecrosis of the right humeral head (arrow) (**a**) and the left humeral head (arrow) (**b**). **c** The chest CT scan (coronary view) showed bilateral osteonecrosis of the humeral heads (arrows), which was more severe on the left side.

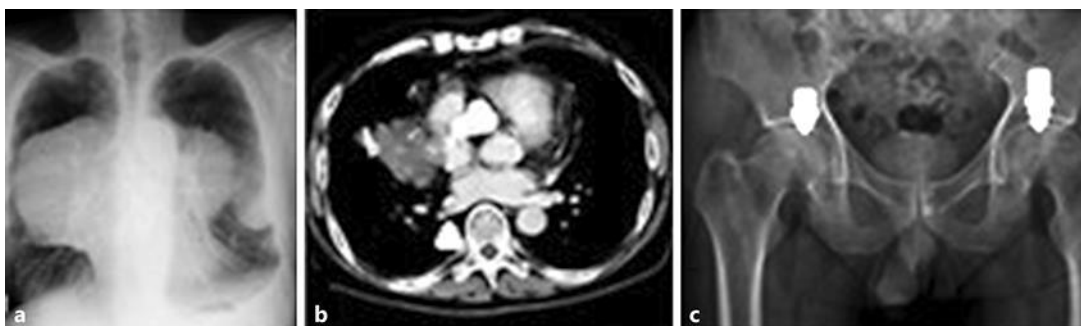


Fig. 3. Case 2 was a 53-year-old male with malignant thymoma who was receiving chemotherapy. **a** The initial chest X-ray showed a large mediastinal mass. **b** The chest CT scan (axial view) revealed a tumor or thrombus over the right posterior proximal pulmonary vein and left atrium (arrowhead). **c** The pelvis X-ray showed bilateral osteonecrosis of the femoral heads (arrows).