

Non-traumatic avascular necrosis of femoral head in malignant disease: Is it disease induced or treatment related?

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Abstract

Avascular necrosis (AVN) of the femoral head is a poorly understood pathologic process often seen with neoplastic process either due to it or its treatment. The pathology is ischaemic bone necrosis and joint collapse or it may be asymptomatic and missed easily. We have described three young patients with AVN. They developed symptomatic AVN within 3 years of treatment while in remission at a stage where a surgical treatment was mandatory.

AVN is under-diagnosed and thus exact incidence is unknown. Non-traumatic AVN occurs usually in young age, may occur early or very late after treatment. The AVN can occur due to malignant process itself or subsequent treatment. The mainstay of management is prompt diagnosis, appropriate prognostication, and justified management. The conservative measures and joint-sparing procedures often fail due to late stage diagnosis. Research to understand the pathobiology of AVN and to develop therapies offers promise for the future successful management. Technological improvements in surgical methods have also improved outcomes and will help patients recover from this functionally debilitating disease.

AVN is an under-diagnosed pathology with high morbidity, and considerable cost of management if diagnosed late. A clinical suspicion in every cancer patient, comprehensive clinical evaluation, early diagnosis and prompt management decrease morbidity, cost and improves management outcome. Appropriate close and focused screening in eligible patients is desirable. Research to understand the pathobiology of AVN and to develop therapies that can be translated to clinical application has progressed.

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Introduction

Avascular necrosis (AVN) of the femoral head is a debilitating yet poorly understood pathologic process consequent to bone ischaemia, as the precarious circulation of the femoral head is compromised. The ischaemia causes necrosis of marrow and osteocytes leading to collapse of the necrotic segment. AVN of the femoral head was initially described by Munro in 1738 and Mankin first reported 27 cases of AVN in 1962.¹ Since then the number of reported AVN cases has increased steadily. The exact prevalence is unknown, but 5-18% of over 500,000 total hip arthroplasties performed annually in USA alone are for AVN of the femoral head.¹ AVN occurs mainly in young adults 35-45 years of age.^{1,2} Males are affected up to three times more than females, and bilateral femoral head AVN is found in up to 75%.¹⁻⁴ Annual Incidence in the late 1990's was reported to be 10 000 to 20 000, but has certainly increased.^{1,2}

The acetabulum is mainly spherical superiorly and allows for approximately 170 degree of coverage of the femoral head. The femoral head is not perfectly spherical, and joint congruity is precise only in the weight-bearing position. The forces that act on the femoral head are varied in different daily life activities. Standing on one leg generates 2.5 times of the body weight across the hip joint, while in running this is increased to 5 X bodyweight across the hip joint. The arterial supply to the femoral head is complex being supplied by multiple sources.³ This arterial supply can be compromised by a variety of traumatic and non-traumatic causes.³⁻⁵

Initially AVN is asymptomatic, but gradually pain and limitation of movement become apparent.^{1,3,5} The pain is commonly localized to the groin area, ipsilateral buttock, knee, or greater trochanteric region; exacerbated by weight bearing and relieved by rest. A straight-leg raise against resistance provokes pain. Passive hip movements are limited, internal and external rotation/abduction of the extended leg (log roll test) may elicit pain. Most cases of AVN are non-traumatic.¹⁻³ Intravascular coagulation is the prime event associated with non-traumatic AVN and may occur secondary to extravascular compression, vessel wall injury

(chemotherapy, radiation), or a thromboembolic event (fat emboli).^{1,5-7} Ischaemia leads to infarcted sub-chondral bone. The weakened and unrepaired necrotic bony trabeculae succumb to weight and mechanical compression, leading to sub-chondral collapse (crescent sign) and, ultimately, articular collapse.^{5,8-11}

The non-traumatic causes of AVN include alcoholism, coagulopathies, systemic chemotherapy, chronic liver disease, corticosteroids, decompression sickness, Gaucher disease, gout, haemoglobinopathy, hyperlipidaemia, idiopathic non-traumatic osteonecrosis, metabolic bone disease, pregnancy, radiation therapy, smoking, systemic lupus erythematosus, DIC, fat embolism syndrome, HIV, deep sea diving, and vasculitis.^{1,3,6,7,12,13} The differential diagnosis of AVN includes trauma, metastatic tumours, osteomyelitis, osteoporosis of head, osteosarcoma, advanced Degenerative Joint disease (DJD), ischaemic fractures, epiphyseal dysplasia, plasma cell myeloma, haemangioma, post radiation changes, sympathetic dystrophy, bone bruise, transient bone syndrome, epiphyseal stress fracture, fracture neck of femur, groin injury, hip dislocation, hip fracture and hip overuse syndrome.^{3,6,7}

The laboratory tests are of minimal value except in connective tissue disorder, hemoglobinopathy, or a coagulation disorder.^{1,9} The radiologic investigations for diagnosis are plain radiographs, MRI, Bone scintigraphy, CT scan and angiography.^{1,7,13} The high rate of bilateral AVN (>60%) and contra-lateral occult disease warrants imaging of the unaffected hip.⁹ The earliest radiographic signs are lucency and sub-chondral sclerosis of femoral head followed by sub-chondral collapse (crescent sign), femoral head flattening and narrowing of articular space.⁹⁻¹³

Radiologic staging of AVN in 4-stage was first proposed by Ficat and Arlet in the 1960s and amended later in the 1970s. Steinberg proposed a more concise and improved staging system, known as Steinberg Classification, which delineates the progression and extent of AVN involvement more precisely in 6 stages.¹⁴

Small medial lesions are considered prognostically favourable. Another commonly used classification system that utilizes MRI and other radiographic modalities is the Association Research Circulation Osseous (ARCO) staging system, which was introduced in 1992.¹⁴

MRI is the most sensitive and specific non-invasive radiologic investigation of choice in symptomatic patients having normal radiographs. It may detect AVN as early as 5 days subsequent to an ischaemic insult.¹⁵

The diagnostic MRI findings include a low signal intensity band (On T1 and T2 images) that demarcates a necrotic femoral head segment. The extent and location of necrosis on MRI is a predictor of femoral head collapse.^{1,16} Smaller lesions (< 25% diameter of the femoral head) and more medial lesions (away from primary weight-bearing areas) predict a better outcome. MRI is indispensable for the accurate staging, as it clearly depict the size of the lesion, and gross estimates of the stage of disease.¹⁶⁻¹⁹ MRI allows sequential evaluation of asymptomatic undetectable lesions. MRI is also capable of imaging in multiple planes and superior soft-tissue resolution.^{17,19} MRI may guide interventional procedures and may demonstrate response to treatment. MRI can also evaluate articular cartilage. MRI facilitates better outcome because of early diagnosis.^{18,19} Microscopic cellular and vascular changes occur earlier than MRI findings. MRI cannot be performed in patients with cardiac pacemakers, intracranial clips, prior hip surgery, or in patients with claustrophobia. It may have diagnostic issues in young children, who may require sedation.²⁰⁻²²

MRI has a higher sensitivity than radionuclide scanning, reported 88% sensitivity, 100% specificity, and 94% accuracy with MRI and 78% sensitivity, 75% specificity, and 76% accuracy with bone scintigraphy.^{15,18,21,22} SPECT scanning had a sensitivity of 91% and a specificity of 78%.

Bone scintigraphy can identify abnormalities earlier than plain radiographs, but should be supplemented with MRI.^{1,18,19} The sensitivity and specificity of Bone scans is lower, but is useful where MRI is contraindicated. SPECT scanning provides images of the radioactivity in 3 dimensions; and eliminates radioactivity resulting from hyperaemia around hip joint and bladder. SPECT is used as an alternative when MRI cannot be performed or is indeterminate. Initially, SPECT may demonstrate an avascular focus, missed with MRI. Collier et al found a sensitivity of 85% for SPECT scanning, and 55% with planar radionuclide imaging.¹⁶⁻¹⁸ With triple-head high-resolution SPECT scanning, Lee et al reported a sensitivity of 97%. However, bone scintigraphy equipped with a pinhole collimator has greater sensitivity.

Computed tomography (CT) scans are less sensitive (sensitivity 55%) than MRI.¹⁸ CT scanning may help delineate early sub-chondral collapse and is more appropriate in evaluating the extent of involvement.^{18,19} CT scans are insensitive for detecting stage 0 and 1 AVN, but they are excellent for detecting femoral head collapse, early degenerative joint disease (DJD), and the

presence of loose bodies.^{18,20,21}

Although less sensitive (sensitivity 41%), plain film radiography may be helpful to assess flattening of the femoral head and associated degenerative changes. Plain film does not detect stage 0 and 1 AVN. A delay of 1-5 years may occur between the onset of symptoms and the appearance of radiographic abnormalities and normal radiographic findings does not exclude AVN.¹⁸ Demineralization of the femur may be detected by densitometry, and Angiography is an investigational invasive diagnostic modality for confirmation of AVN.^{18,21,22}

Conservative non-surgical management provides temporary symptomatic relief only, without affecting the progressive course of AVN.²³ Ultimately AVN leads to femoral head collapse in 2-3 years (67% of asymptomatic cases and 85% of symptomatic cases). A prophylactic (decompression, grafting, or osteotomy) or reconstructive surgery (arthroplasty

- total hip replacement or THR) is the treatment of choice.^{18,19}

Case Reports

Case-1

A 27 year old unmarried male presented in October 2009 with vague chest pain, dry cough, asthenia and

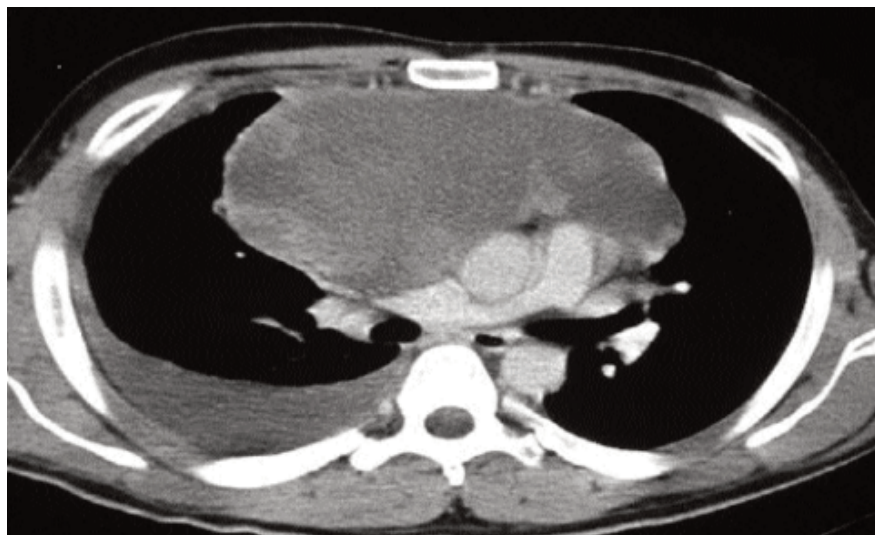


Figure-1: Contrast enhanced CT scan of the chest demonstrates a large anterior mediastinal cystic mass encasing the aorta and pulmonary artery, along with moderate right sided pleural effusion.

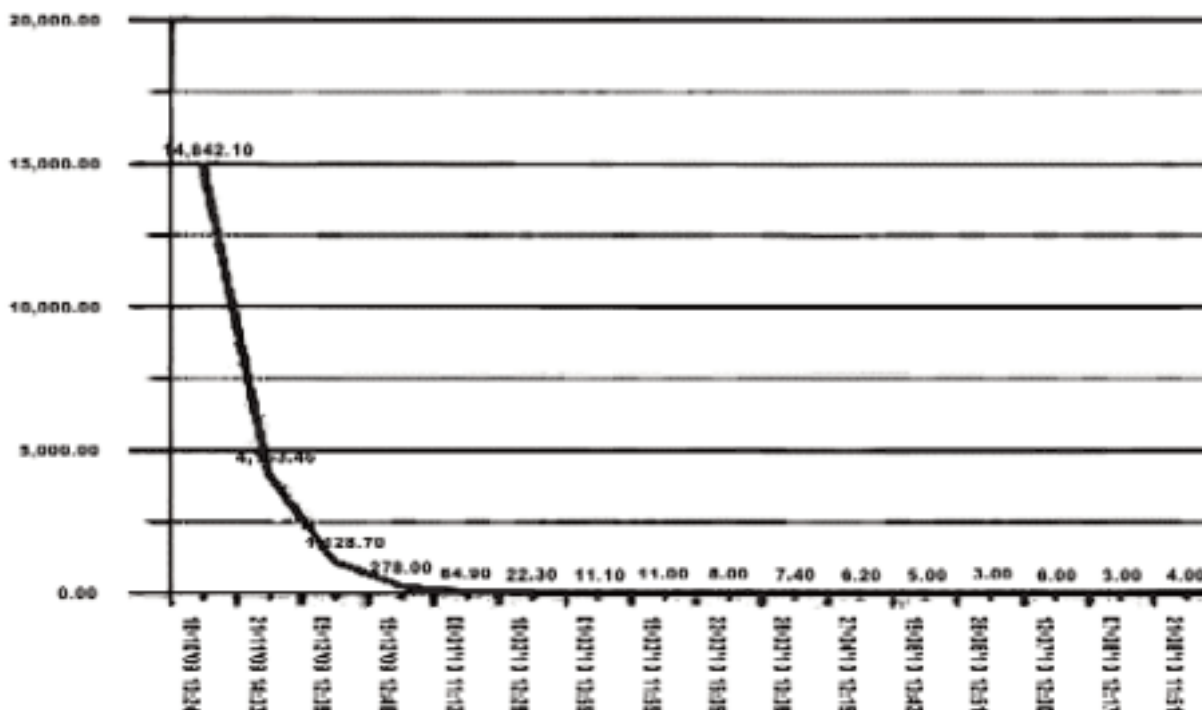


Figure-2: AFP level decline after Chemotherapy.

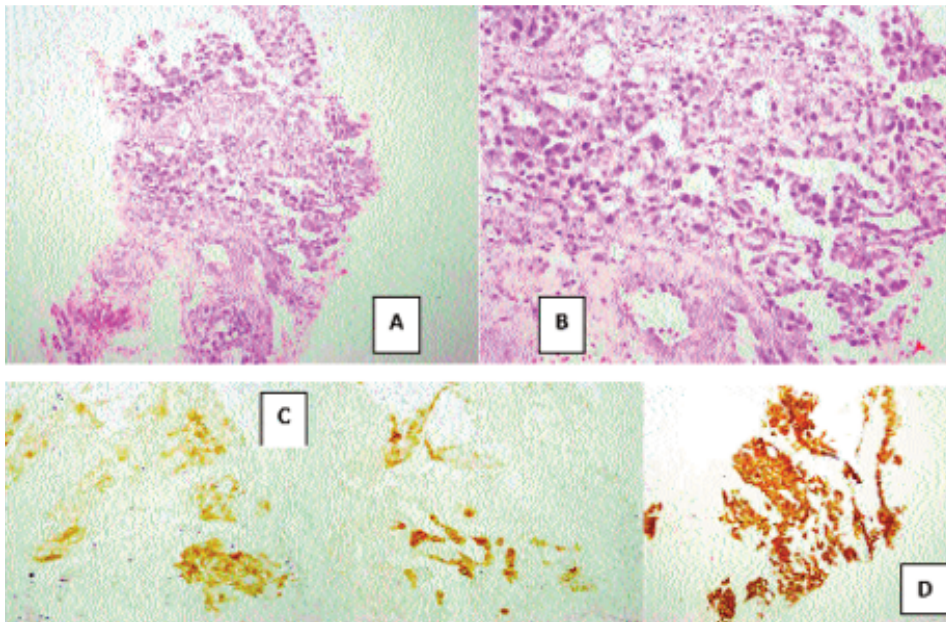


Figure-3: Fibrocollagenous tissue infiltrated by cells with vacuolated cytoplasm, pleomorphic nuclei and prominent nucleoli HE x10 obj, (A), HE x40 obj (B), Alfa feto protein (C) and Pan cytokeratin (D) positivity.

significant weight loss of one month duration. Initial performance status was 4 on WHO scale. His initial CT scan chest showed a 15 x 8 x 20 cms heterogeneous enhancing mass with a small focus of calcification, displacing SVC and vessels posteriorly. There was right pleural effusion and mild ascites (Figure-1). Serum LDH

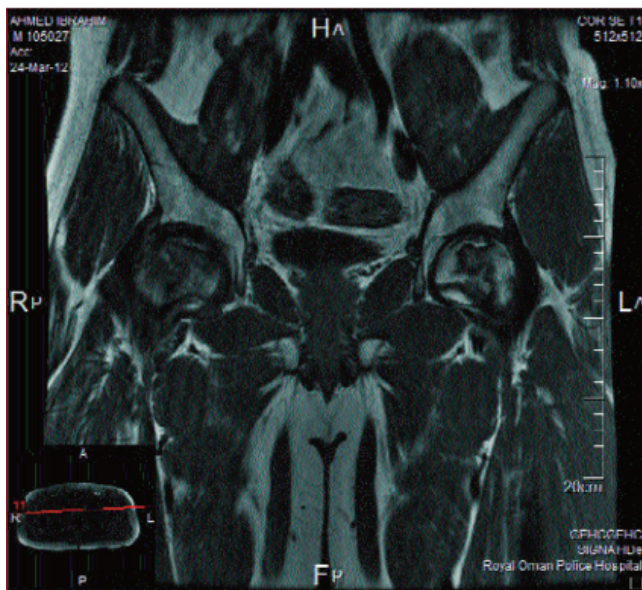


Figure-4: Coronal T1-weighted (T1W) MRI image of the pelvis in a patient with bilateral avascular necrosis of the femoral head shows increased signal within the superior aspect of the femoral head, representing fat, surrounded by a line of decreased signal, representing sclerotic reactive margin.

was 452 (N<190), while pleural fluid LDH was 951 iU/L. Beta HCG was <1 iU/L and AFP was 14842.1 ug/L (N= 0-15). Echocardiogram was unremarkable. A CT guided biopsy showed features consistent with non-seminomatous germ cell tumour (Positive for PLAP, CK and AFP. Negative for CD30). Pleural fluid cytology was Negative for malignant cells. His bone marrow examination was negative for bone marrow infiltration. A PET CT scan showed diffuse increased metabolic activity in large soft tissue anterior mediastinal mass, along with central necrosis. AFP (Alpha fetoprotein) escalated to 16858 ug/L.

The case was discussed in multi-disciplinary tumour board and decided to start him with systemic therapy followed by radiotherapy consolidation, according to response assessment. Patient was counselled and started with BEP chemotherapy which he tolerated well. A PET CT scan after 4 cycles of BEP, showed 11 x 5 cms partly necrotic yet metabolically active tumour mass in anterior mediastinum. His tumour markers AFP and LDH were normalized (Figure-2). He was given additional 2 cycles of 3 weekly paclitaxel and carboplatin and then referred to cardiothoracic surgeon, for possible resection of residual mass. Surgery was deferred due to proximity of tumour to major vessels.

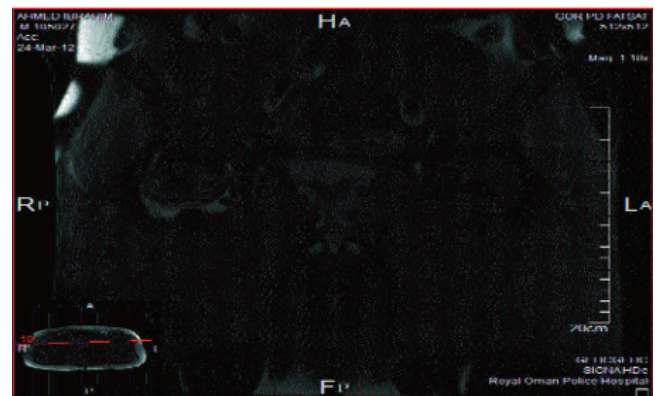


Figure-5: A Coronal T2-weighted fat suppressed image demonstrates bilateral ring like sub-chondral area, a features of avascular necrosis.

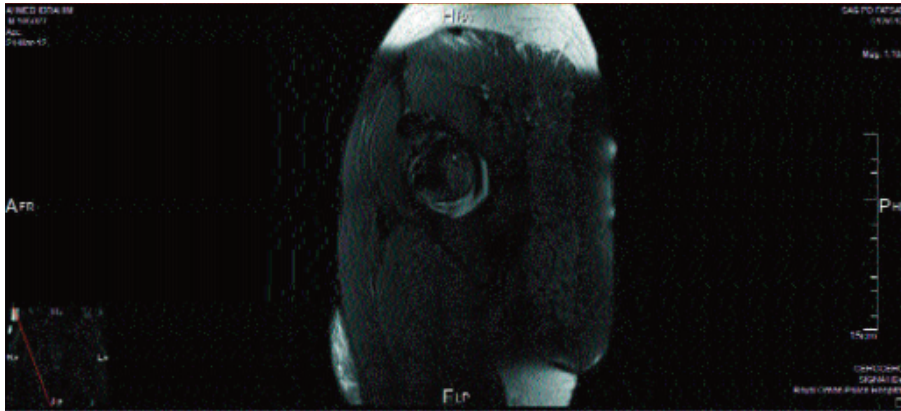


Figure-6: A sagittal T2 fat suppressed image of the left hip joint demonstrates a crescent sign and cortical collapse, representing avascular necrosis.

He was given Gemcitabine plus Oxaliplatin as 3rd line chemotherapy in 2010. A PET scan after C3 showed a 7 X 5 cms necrotic anterior mediastinal mass with a peripheral rim of FDG activity. He finished C6 and was referred for surgery again. A surgical resection (anterior mediastinal tumour) was done in December 2010. The operative findings were a large (10x5 cms), hard, solid (no cystic areas), extra-pericardial tumour. It was not adherent to any major vessels, but was extending to right pleural cavity and right dome of diaphragm. The histopathology showed 11x7x5.5 cms necrotic partly calcified mass, with fibrous tissue infiltrated by macrophages and foreign body giant cells, consistent with post-chemotherapy changes (Figure-3).

He was since then on regular follow up with CT and PET imaging showing no evidence of disease. He is not diabetic, no evidence of hyperlipidemia, no congenital disease, and no history of trauma or infection. There was no known risk factor of non-traumatic AVN. In February 2012 he started having bilateral hip pain exacerbated by movement and activity or prolonged standing. CT scan and MRI showed radiologic changes consistent with bilateral avascular necrosis of femoral heads i.e., oedema, effusions, granulation tissue crescent sign and fracture (Figure-4, 5 and 6). He underwent right hip replacement (THR) in August 2012. The biopsy showed necrosis of cortical bone, regenerative process in surrounding tissues, increased osteoclastic activity, bone marrow oedema, haemorrhage, fibrillo-reticulosis, and hypocellularity. Adipocytes in marrow were replaced by eosinophilic debris. The histopathology of resected lesion did not show any evidence of osteoporosis, metastasis or tuberculosis. The Left hip replacement decision was initially deferred, but had contralateral left THR as well in November 2015. The patient has periodic

and regular follow up with serial clinical, serologic and radiologic evaluation. He was last seen in October 2016 with no evidence of disease clinically, serologically or radiologically. He is asymptomatic and has normal routine life, performance status of 0 (100%) and efficiently performing the job as a policeman.

Case-2

A 32 years married female, normotensive and non-diabetic, initially presented with progressive muscle weakness and ptosis of few months duration in 2011. The radiologic evaluation by pan CT scan suggested a thymic growth. A CT guided biopsy confirmed a thymic carcinoma. She underwent radical surgery. As per disease stage and positive capsular invasion, she received post-operative radiotherapy (without any concurrent chemotherapy) 50.4 Gy in 28 fractions from 28/07/2012 to 05/09/2012, by IMRT. A post-radiotherapy PET CT Scan did not show any residual disease. The patient became pregnant, so a chemotherapy decision was deferred. The pregnancy unfortunately ended in abortion. The role of adjuvant chemotherapy was discussed with the patient, as elapsed time from surgery was long enough to justify adjuvant chemotherapy. Due to uncertain and questionable benefit patient was not keen to receive chemotherapy and opted to remain in close clinical and radiologic follow up. There was no risk factor for non-traumatic AVN.

She developed pain and difficulty in walking and gradually became wheelchair bound in 2015, without any history of trauma or infection. Clinical evaluation and MRI confirmed bilateral avascular necrosis of femoral neck. A CT Scan in February 2015 in Thailand was negative for any disease relapse. A PET scan in Dec 2015 confirmed her malignant disease in remission. She proceeded with bilateral hip replacement as two step surgery, one after the other. She was last seen in clinic in September 2016 and was in remission.

Case-3

A 49 years female, with no co-morbid conditions, presented in November 2015 with epigastric pain and weight loss. An initial Pan CT scan showed a gastric mass 11 cms in length and 3 cms in depth on lesser curve and posterior wall of stomach, with loss of fat

planes along left hepatic lobe. There were few sub-centimeter local lymph nodes. Liver, lungs and bones were free. OGD (Esophago-gastro-duodenoscopy) showed a fungating mass which turned out to be poorly differentiated adenocarcinoma strong positive to AW1/AE3 and CK7 on histopathology and immunohistochemistry. She sought a second opinion abroad where OGD and Scans were repeated and was advised neoadjuvant chemotherapy to start with, the same opinion as in our institute. She received 3 cycles of EOX (Epirubicin, oxaliplatin, Xeloda/capecitabine) based chemotherapy with poor tolerance and a subsequent 15% dose reduction. A post 3 cycles CT scan showed no significant response though CA19-9 dropped from 347 to 63. The case was discussed in MDT board and planned for a surgery. She finally underwent robotic assisted subtotal gastrectomy abroad in March 2016. Final histopathology was Adenocarcinoma grade IV, positive proximal margin R1, 20/22 lymph nodes positive for metastasis, while omentum was free. She was offered Concurrent chemo-radiotherapy as per our protocol (IMRT 45Gy with 5FU), which she finished in July 2016. A post treatment PET scan was negative in August 2016. She developed left thigh and lower limb pain. An MRI was done and showed focal subarticular bone marrow oedema of left femoral head, no soft tissue abnormality or no joint abnormality all consistent with avascular necrosis. She underwent Left THR in September 2016. She was last seen in September 2016 and was in complete remission.

Discussion

AVN, first described by Munro in 1738, is a poorly understood and clinically under estimated pathologic process.^{1,3,5} Its initiation and progression is influenced by multiple factors ultimately resulting in femoral head ischaemia and necrosis.^{1,3,6,8,9} It is believed that up to 18% of hip replacements done are due to AVN.^{1,10} The Non-traumatic causes are predominant yet under-appreciated clinically. Most of these cases are seen in young cancer survivors, believed to be due to prolonged chemotherapy and high cumulative doses of steroids.^{6,7} The childhood survivors of lymphoma, leukaemia and sarcoma have a strong predisposition, up to 2.8% cumulative incidence⁷ and more prevalent post bone marrow transplant.¹¹ AVN is reported as early as 1month to as late as 18 years post chemotherapy.^{1,6,7,10} It is more likely to be seen in young males, probably reflecting physical stress and activity. Patients receiving dexamethasone compared to prednisolone have a 30% higher risk.^{1,4,7} The dose of steroids used, and age at diagnosis are significant

contributory factors. Radiation to gonads, both male and female resulting in decreased circulating hormonal levels, is an additional risk factor described.^{2,13} The mean time from diagnosis of AVN to arthroplasty is 1.3 years.^{12,20,25} It has been reported that 54-80% of renal transplant recipients get bilateral AVN detected often with plain radiographs.²⁰ There are other factors, some known many yet known, in malignant disease in addition to chemotherapy and radiotherapy that may contribute to AVN. The known ones are hyperlipidaemia, DIC, coagulation defects, changes in vascular integrity, TNF, etc. There are many new yet unknown factors including the long term effects of new targeted therapies and drug interactions.^{2,3,5,6,20}

We report three cases of AVN in one adult young male and two females. The male patient received 3 lines of chemotherapy. He developed symptomatic bilateral AVN within 2 years after treatment, which is not usual. He had a post chemotherapy completion surgery for his primary disease. He underwent sequential bilateral THR and is having a comfortable life with good performance status and normal activities. The second female patient on the other hand did not receive any chemotherapy at all. She only received radiotherapy, and that was also to mediastinum far away from hip joints. She developed bilateral AVN within 3 years of completion of adjuvant radiotherapy after surgical management. She also proceeded for two step bilateral THR. The third female received chemotherapy and radiotherapy and immediately post treatment developed symptomatic AVN, and underwent unilateral THR.

Treatment of avascular necrosis (AVN) has been facilitated by the adoption of a uniform international classification system,¹⁴ by effective early diagnosis using magnetic resonance imaging (MRI), and by more aggressive surgical management.^{16,18,25} No universal satisfactory therapy has been developed, for early disease. Measures to preserve the joint are associated with better prognoses when the diagnosis is made early. Early diagnosis provides a greater chance of success of conservative treatment. Patients who are at high risk must be screened regularly and periodically using MRI, as normal radiograph findings do not exclude AVN. The results of joint replacement therapy are poor in younger age than in older patients. It is thus critical to diagnose AVN at an early stage to prevent or delay disease progression. Failure to diagnose this potentially devastating condition (AVN) in a young patient has the potential for serious morbidity and medical-legal repercussions.²³⁻²⁵ Malpractice settlements reflect compensation for a lifetime of a

potentially compromised lifestyle with much morbidity. Failure to pursue this condition with more aggressive imaging in a high-risk population can potentially lead to medical malpractice.

Some of the recent efforts have focused on the use of cellular therapies for osteonecrosis. These include transplanting CD34+ cells, known to be both vasculogenic and osteogenic, after G-CSF mobilization. Several studies have attempted to treat osteonecrosis by transplanting exogenous stem cells (MSCs) either systemically or locally, or biphasic calcium phosphate (BCP) ceramic scaffolds seeded with MSCs on inducing osteointegration and new bone formation.^{24,25} Osteonecrosis research has focused on the effectiveness of bisphosphonates, growth factors, lipid-lowering agents, and combined drug therapies. Lipid-lowering drugs such as statins decrease the incidence of steroid-induced osteonecrosis. Other studies have also shown that the simultaneous use of anticoagulants and lipid-lowering agents can be protective from steroid-induced osteonecrosis. The impact of such combination drug therapies is yet to be fully evaluated.²⁵ Clinical studies are focusing to improve older surgical techniques and evaluate novel techniques for treatment of osteonecrosis. Trans-trochanteric rotational osteotomy has demonstrated variable success for avoidance of femoral head collapse. Advancements in hip resurfacing have made it a viable potential option in young patients under the age of 25 years reducing the need for THA.²⁵ There are however risks of ionic wear, fracture, and loosening. Total hip arthroplasty has undergone technical improvements and implant survival is now much higher. Uncemented ceramic-on-ceramic THA has demonstrated some promise for improved outcomes and implant durability. Improved micro-surgery has enhanced outcomes for free vascularized fibula grafting to the osteonecrosis hip.^{24,25} Other grafting techniques, such as bone graft pedicled with quadratus femoris in a titanium mesh, have also been developed, but long-term effectiveness need validation.^{24,25}

It is believed that incidence of avascular necrosis (AVN) is increasing. It is expected that more and more cases of AVN will be seen in future in oncology practice due to better awareness and diagnoses, improved survival, prolonged use of chemotherapy, higher number of patients going for organ or marrow transplant, more use of anti angiogenic drugs and multi kinase inhibitors, more use of radiation therapy, prolonged use of steroids (higher cumulative dose), immunosuppressive therapy, osteoporosis inducing

drugs, and use of bisphosphonates.^{1,20}

The AVN has a higher morbidity, and substantial cost of management. A clinical suspicion and symptom query at clinical evaluation is the index to early diagnosis and management. Focused screening in transplant patients, older patients, patients having prolonged chemotherapy, and gonado-toxic therapy is desirable.^{20,23} Non-traumatic Osteonecrosis is a pathology commonly seen in young adults, where collapse of the femoral head and early onset of osteoarthritis may eventually necessitate hip arthroplasty. The conservative measures and joint-sparing procedures usually fail due to late stage diagnosis. Basic science research to understand the pathophysiology and to develop therapies that can be translated to clinical application has progressed. These advances offer promise for the future successful management of osteonecrosis. Technological improvements in surgical treatment methods have also improved outcomes over the time and will continue to help patients recover from this functionally debilitating joint disease.²⁵

Conclusions

AVN is an under-diagnosed pathology with high morbidity, and cost if managed late. The conservative measures and joint-sparing procedures usually fail due to late stage diagnosis, mandating an early diagnosis. A clinical suspicion in every cancer patient, comprehensive clinical evaluation, early diagnosis and prompt management decrease morbidity, cost and improves management outcome. Appropriate close and focused screening in eligible patients is desirable. Research to understand the pathobiology of AVN and to develop therapies that can be translated to clinical application has progressed. These advances offer promise for the future successful management of osteonecrosis. Technological improvements in surgical treatment methods have also improved outcomes over the time and will continue to help patients recover from this functionally debilitating joint disease.

Disclaimer: Abstract has NOT been previously presented or published in a conference, NOR manuscript was part of a research, PhD or thesis project.

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Consent: The consent of all three patients was taken who are described in the manuscript, but even then the identity of patients is remained unrevealing anywhere.

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