

# MULTIFOCAL OSTEONECROSIS AFTER SHORT TERM

## METHYLPREDNISOLONE THERAPY—CASE REPORT

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### BACKGROUND

Aseptic necrosis or osteonecrosis is a condition that occurs when the blood supply to the bone is disrupted. This leads to death of osteocytes, dead tissue reabsorption and overall osseous tissue weakening, which can lead to subchondral fractures and collapse.

The pathophysiological mechanism of the development of osteonecrosis involves multiple factors. Increased differentiation of bone marrow cells into adipocytes, abnormality of lipid metabolism and clotting events, decreased angiogenesis and elevated vasoconstriction, oxidation injuries and finally a genetic predisposition; are

### OBJECTIVES

- To present a case of iatrogenic induced multiple osteonecrosis from high methylprednisolone treatment, the second case at the Pediatric Hospital, "Mother Teresa" University Hospital Center.
- To present the clinical state of the patient and the evolution.
- To address the preventing measures and management approach, since corticosteroids are widely used in clinical prac-

### CLINICAL PRESENTATION

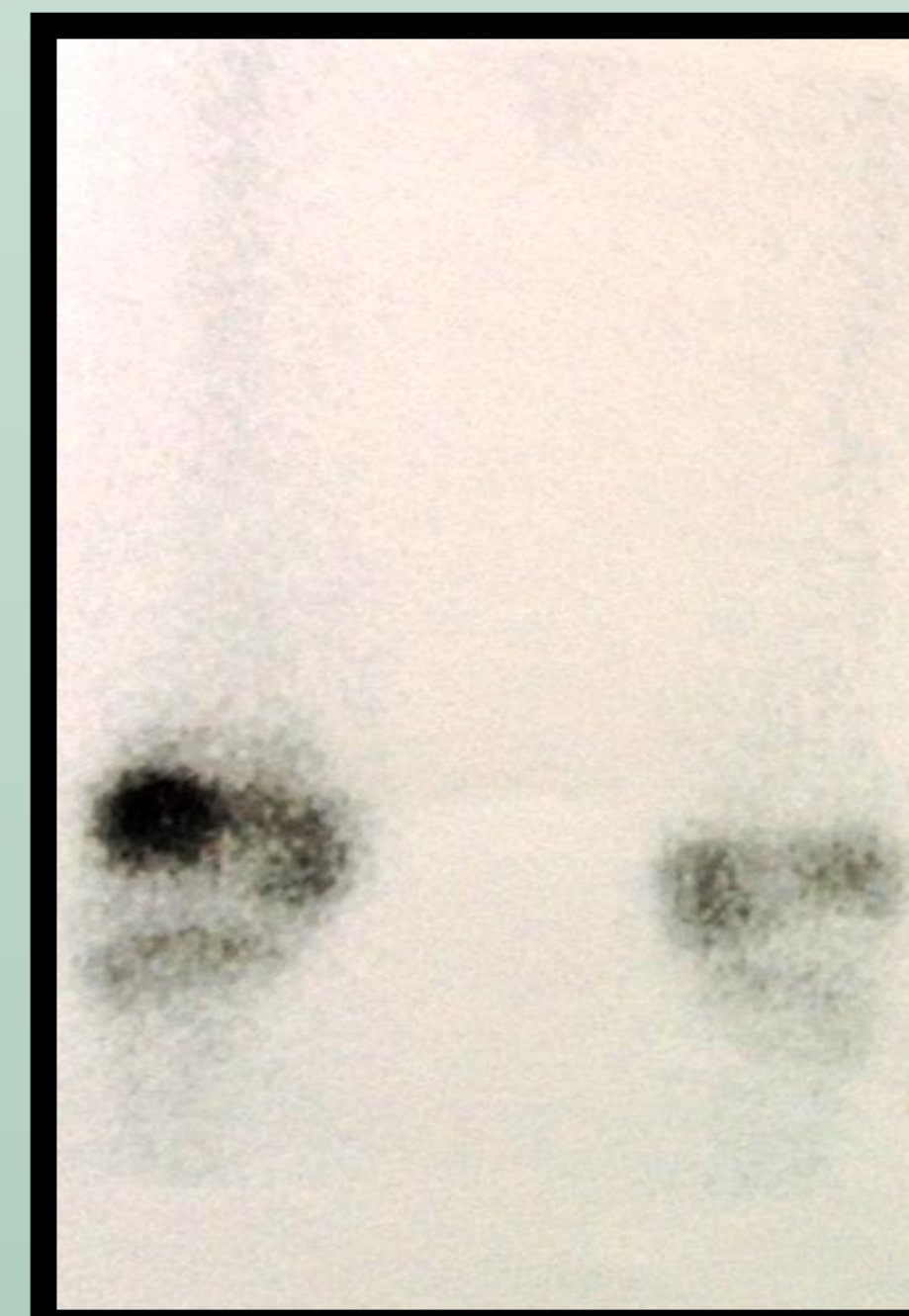
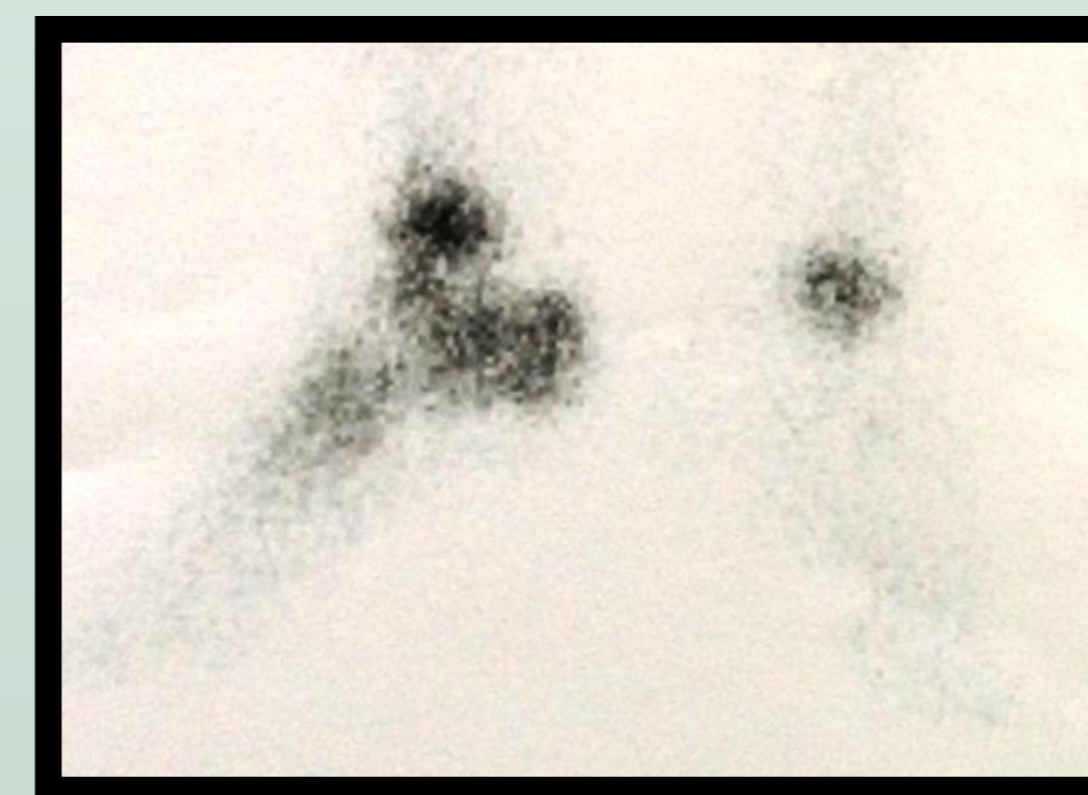
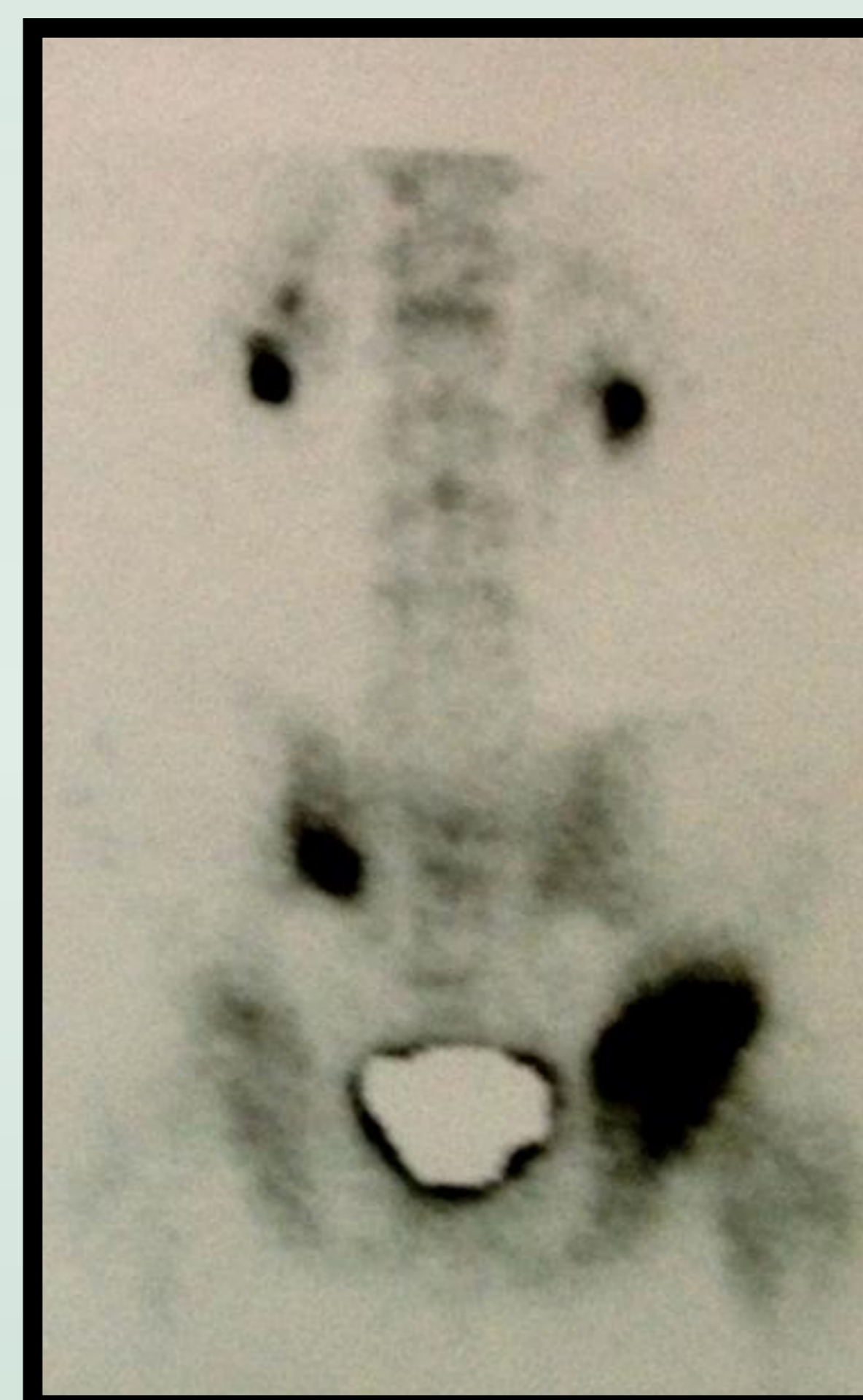
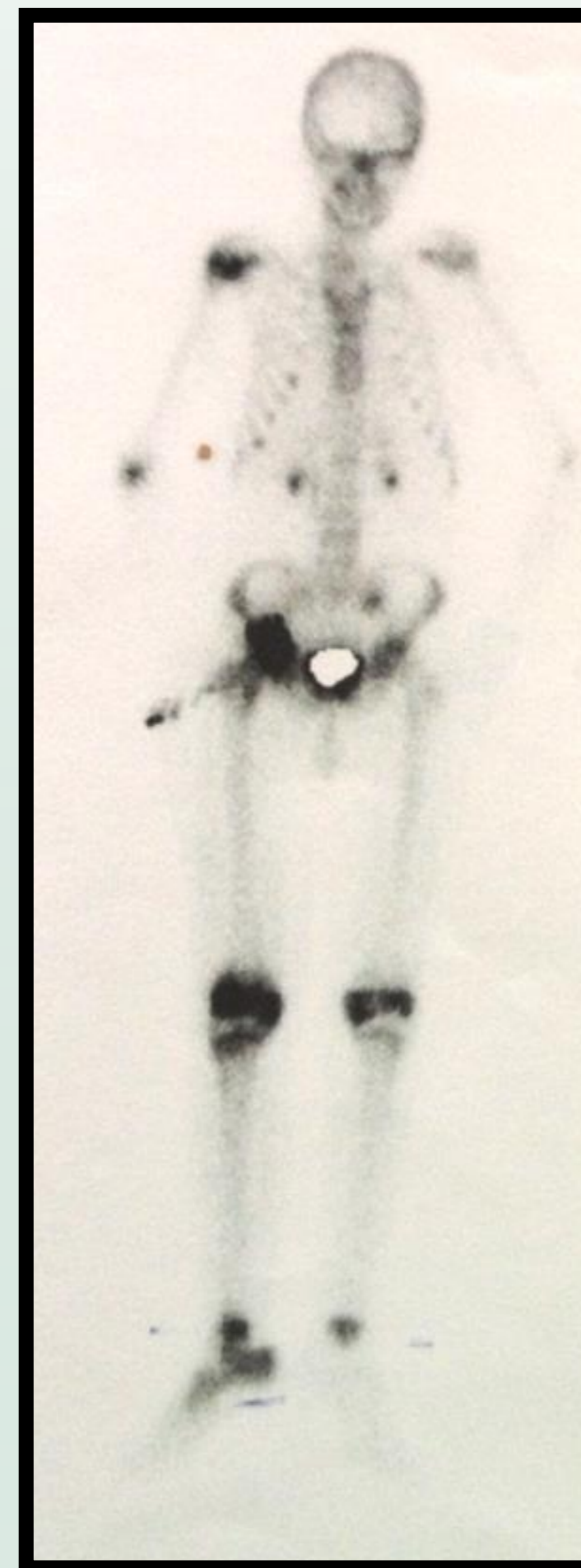
The patient A.N. is diagnosed with **Craniopharyngeoma** at the age of four years old and undergoes **three neurosurgical interventions** because of the tumor's **recidivism**. The third intervention is at the age of six years old.

The patient presents at our clinic at the age of five and a half years old, after his second neurosurgical intervention when he presents with **left hemiconvulsions**. AED therapy with **Carbamazepine** therapy is started and is continued for 5 years. During this time the child remains seizure free and the CBZ is terminated. Six months after the AED termination the child presents **generalized seizures refractory** to treatment. **Valproic acid** is started followed by **Lamotrigine**. The seizures stop.

One month later, at the age of fifteen years old the patient manifests a hypersensitivity skin reaction with **erythema multiforme and generalized desquamation** of the skin. Diagnosis of Lamotrigine induced **Stevens-Johnson syndrome** is made and the child is inappropriately admitted at the adult dermatology clinic where he is treated with **IV Methylprednisolone, 150mg/day for 4 weeks**. During the last days of treatment, the boy feels severe back pain while walking, falls in the ground on his knees and is unable to walk anymore. At this moment he gets admitted at our clinic.

At the moment of admission, **the condition and overall state of the patient were dramatic and severe**. Marked **Cushingoid appearance** is noticed. The **skin features hyper pigmented maps and striae** all over the body, with a predominance on the lower extremities. Knee joints and talo-crural joints were severely painful and edematous, dexter>sinister. Palpation of abdomen showed **hepatomegaly**, 4-5 cm under the rib cage. Neurological exam showed **bilateral tremor and left pyramidal syndrome**.

A **multidisciplinary team** is gathered to evaluate the situation and a panel of **laboratory assays and imaging studies** are ordered, with results and short comments as follow:



- CBC, Biochemical panel, Blood Electrolytes, Coagulation tests: without significant changes.
- Hormonal panel and pituitary axis show normal levels of TSH, ACTH and Cortisol.
- Adrenal and Heart ultrasound: normal.
- Bone marrow examination shows normal marrow activity.

### PTH=250 pg/ml

- Flow cytometry shows iatrogenic **immunodeficiency** with marked **T cell and NK cell depletion**: CD<sub>4</sub>=16.7% NK=2%
- Evolution of C-Reactive Protein during admission: CRP<sub>1</sub>/CRP<sub>2</sub>/CRP<sub>3</sub>=254/112/41 (mg/dl)
- Abdominal Ultrasound: Hepatomegaly (13.5 cm).
- **Bone Scintigraphy: Multiple osteonecrosis.**
- Knee Joint US: Bilateral edema/fluid accumulation.
- **Pelvic CT: Bilateral osteonecrosis of femoral heads, dex>sin.**
- **Right Knee Joint MRI: Multiple osteonecrotic lesions** at the femoral diaphysis and tibia epiphysis.

### TREATMENT AND MANAGEMENT

- Anti resorptive therapy is initiated with **bisphosphonates**. Pamidronic Acid 60mg over the course of 3 months. **Calcium** supplementation + Vit **D3** 3600 UI/day
- Pain management: **Ibuprofen**, up to 1200mg/day
- Gastric protection: **Omeprazol** 40mg/day
- **Immunoglobulin** therapy: IVIg Pentaglobin, (one cycle).
- AED therapy with Valproate and Clobazam.
- Bed rest.
- The patient gets transferred to a specialized center in Germany for orthopedic treatment.

### DISCUSSION

The literature is poor regarding prevention of osteonecrosis. Multiple agents and methods have been tried in animals with promising results but controlled human studies are absent. The agents and methods used in animal studies include: Lipid lowering drugs (Lovastatin), anticoagulants (warfarin, enoxaparin), anti-oxidants (Vitamin E), Nitrate patches, Lipoic Acid, Hepatic CYP3A inducer to increase the rate of glucocorticoid metabolism, Electromagnetic fields and Intra-bone marrow injection of autologous bone marrow cells. Future controlled trials are needed to

Studies in rabbits have confirmed that IV corticosteroid therapy is highly associated with osteonecrosis. Furthermore, the risk seems to be significantly higher with IV methylprednisolone (compared to other glucocorticoids). The choice of the corticosteroid must be weighted according to benefits and risks. Similar drugs within the glucocorticoid family with the same effectiveness profile may be considered.

### REFERENCES

- L. Qin, G. Zhang, H. Sheng, K.W. Yeung, H.Y. Yeung, C.W. Chan, et al. Multiple bioimaging modalities in evaluation of an experimental osteonecrosis induced by a combination of lipopolysaccharide and methylprednisolone. *Bone*, 39 (2006), pp. 863-871
- P. Kang, H. Gao, F. Pei, B. Shen, J. Yang, Z. Zhou Effects of an anticoagulant and a lipid-lowering agent on the prevention of steroid-induced osteonecrosis in rabbits. *Int J Exp Pathol*, 91 (2010), pp. 235-243
- T. Mikami, T. Ichiseki, A. Kaneuji, Y. Ueda, T. Sugimori, K. Fukui, et al. Prevention of steroid-induced osteonecrosis by intravenous administration of vitamin E in a rabbit model. *J Orthop Sci*, 15 (2010), pp. 674-677
- T. Asada, T. Koshida, M. Umeda, K. Ono, H. Matsuya, T. Wada, et al. Prevention of corticosteroid-induced osteonecrosis in rabbits by intra-bone marrow injection of autologous bone marrow cells. *Rheumatol (Oxford)*, 47 (2008), pp. 591-596
- K.N. Mallos, A.H. Karantanas, S.E. Vartimidis, Z.H. Dallana, K. Bargiotas, T. Maris Osteonecrosis of the femoral head: etiology, imaging and treatment. *Eur J Radiol*, 63 (2007), pp. 16-28
- R. Aaron Osteonecrosis: etiology, pathophysiology and diagnosis. *J. Callaghan, A. Rosenberg, H. Rubash (Eds.), The adult hip*, Lippincott-Raven, (1998)
- H. Sheng, G. Zhang, Y.X. Wang, D.K. Yeung, J.F. Griffith, K.S. Leung, et al. Functional perfusion MRI predicts later occurrence of steroid-associated osteonecrosis: an experimental study in rabbits. *J Orthop Res*, 27 (2009), pp. 742-747
- V. Gangji, M. Toungouz, J.P. Hauzeur Stem cell therapy for osteonecrosis of the femoral head. *Expert Opin Biol Ther*, 5 (2005), pp. 437-442
- P. Hernigou, A. Poignard, D. Manicom, G. Mathieu, H. Rouard The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. *J Bone Jt Surg Br*, 87 (2005), pp. 896-902
- T. Yamamoto, T. Ito, Y. Sugitaka, K. Suetishi Effects of pulse methylprednisolone on bone and marrow tissues: corticosteroid-induced osteonecrosis in rabbits. *Arthritis Rheum*, 40 (1997), pp. 2055-2064
- T. Mikami, T. Ichiseki, A. Kaneuji, Y. Ueda, T. Sugimori, K. Fukui, et al. Prevention of steroid-induced osteonecrosis by intravenous administration of vitamin E in a rabbit model. *J Orthop Sci*, 15 (2010), pp. 674-677
- T. Masuda, K. Iwakiri, Y. Oda, Y. Kaneshiro, H. Iwaki, H. Ohashi, et al. Increased hepatic cytochrome P4503A activity decreases the risk of developing steroid-induced osteonecrosis in a rabbit model. *J Orthop Res*, 26 (2008), pp. 91-95
- K.A. Lai, W.J. Shen, C.Y. Yang, C.J. Shao, J.T. Hsu, R.M. Lin The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis: A randomized clinical study. *J Bone Joint Surg Am*, 87 (2005), pp. 2155-2159
- M. Ajmal, A.J. Matas, M. Kuskoewski, E.Y. Cheng Does statin usage reduce the risk of corticosteroid-related osteonecrosis in renal transplant population? *Orthop Clin North Am*, 40 (2009), pp. 235-239

