

Multi-joint steroid-induced avascular necrosis in a malignant brain tumor patient

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Practice points

- Avascular necrosis is a rare but serious adverse event associated with the use of corticosteroids for long durations or at high doses.
- This case report highlights the extent to which multi-joint avascular necrosis can occur in patients with brain tumors following a short course of low-dose corticosteroids.
- Careful evaluation of and monitoring for the development of avascular necrosis should occur routinely in patients with primary or metastatic brain tumors, given the frequent use of corticosteroid therapy for symptom management in this population.

Avascular necrosis (AVN) is a rare but serious adverse event associated with the use of corticosteroids for long durations or at high doses. This case report describes a 47-year-old female patient with low-grade astrocytoma who was initiated on low-dose dexamethasone for symptom management. The patient developed joint pain 1 year after steroid exposure, then was found to have AVN of the hip followed by multiple other joints. This case report highlights the extent to which AVN can occur in patients with brain tumors following a short course of low-dose corticosteroids. Careful evaluation of and monitoring for the development of AVN should occur frequently in patients with brain tumors given the frequent use of corticosteroids for symptom management in this population.

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Between 2012 and 2016, the annual average age-adjusted incidence of malignant brain tumors in the USA was 7.08 per 100,000 [1]. The clinical presentation and symptoms associated with malignant brain tumors are often related to position, size and classification of brain tumor [2]. Symptoms may be described as general, including seizures and headaches, or focal, including gait abnormalities and vision changes [2]. Corticosteroids have played a key role in the management of primary and metastatic brain tumor symptoms that are related to edema and increased intracranial pressure for over 50 years [3,4]. Dexamethasone is the most widely utilized steroid in this setting, in large part due to its long half-life and minimal mineralocorticoid activity compared with other steroids [3,5]. However, despite routine use of steroids, there are limited data from randomized trials to evaluate the optimal dosing, duration and tapering schedule for patients with brain tumors. Commonly reported doses of dexamethasone in the literature range from 4 to 24 mg (daily oral divided doses), with tapering based on symptom resolution, patient tolerability and provider preferences [6–8].

While dexamethasone has changed the landscape of symptomatic management of patients with malignant brain tumors, the use of steroids is not without potential consequence. Common steroid side effects include hyperglycemia, insomnia, mood changes, myopathy, acid reflux, immunosuppression and many others [3,5,9]. A rare but serious side effect that can occur as a result of steroid use is avascular necrosis (AVN) or osteonecrosis, most commonly affecting the hip joint [9,10]. AVN is commonly associated with high-dose or long-term corticosteroid use [10]. Steroid use is the most common cause of nontraumatic osteonecrosis of the hip [11]. The mechanism for

steroid-induced AVN is thought to be multifactorial compromise in bone vasculature which may be caused by the following proposed mechanisms: fat embolization, intravascular coagulation and/or osteocyte apoptosis [11]. AVN may present as deep joint pain and/or impaired joint mobility for patients, and symptoms are often relieved with rest [12]. AVN is diagnosed via CT scan or MRI [11,12]. The mainstays of treatment for AVN are surgical interventions that range from core decompression to joint replacement [11,12].

In this case report we describe a patient with a malignant brain tumor who developed bilateral multi-joint AVN (MJAVN) following a short course of low-dose corticosteroids.

Case presentation

In July 2015 a 47-year-old female patient presented to her primary care provider (PCP) for persistent, severe left ear pain that radiated to her jaw. The following day, she developed left-sided facial swelling and blurred vision in the left eye. These acute symptoms caused the patient to present to the emergency department, where she underwent imaging; an MRI scan demonstrated a non-enhancing, T2-hyperintense, right insular lesion. Surgical biopsy of the lesion was obtained and confirmed WHO grade II astrocytoma. Prior to this PCP visit, the patient was in good health and had a past medical history significant for early-onset menopause at 38 years of age.

Upon diagnosis of the WHO low-grade astrocytoma, the patient was initiated on oral dexamethasone 4 mg twice daily for 14 days and was then decreased to 2 mg twice daily for 12 days. The patient experienced increased appetite, weight gain, irritability and mania while on dexamethasone. Due to intolerable side effects, dexamethasone was immediately discontinued, and the patient's corticosteroid regimen was transitioned to hydrocortisone 20 mg every morning and 10 mg every evening (comparable to 1.1 mg of daily dexamethasone equivalents [DDE]) for 10 days. The patient underwent surgical resection of the astrocytoma in September 2015. Post-resection, the patient was re-trialed on dexamethasone, starting with 10 mg every 6 h for the first 4 days postoperatively. Unfortunately, within 3 days, the patient developed the same side effects as previously, prompting the immediate discontinuation of dexamethasone. She then developed excessive fatigue, myalgias throughout her body, loss of appetite, headaches and nausea, which prompted concern for adrenal insufficiency. She was started on hydrocortisone 20 mg every morning and 10 mg every evening (1.1 mg DDE) and referred to the endocrinology department. The patient continued hydrocortisone for 14 days and was tapered off after a normal cortisol stimulation test and symptom improvement; her dose was decreased by 5 mg (0.2 DDE) every 2 weeks. During this time, she had ongoing monitoring of her low-grade astrocytoma via surveillance MRI scans and specialty follow-up with neuro-oncology every 3 months.

By December 2015 the patient had completely tapered off steroids but began to complain of diffuse myalgias and arthralgias. This complaint was not mentioned again until June 2016, at which time the patient developed acute hip pain; imaging with her PCP demonstrated arthritis. Upon further workup, the patient was found to have bilateral AVN of both hips, with a minimal left subchondral impaction fracture of the femoral head. In November 2016 she underwent right total hip replacement surgery, followed by left total hip replacement in March 2017. In September 2017 the patient was found to have AVN of her left knee and had a left total knee replacement the following month. She was found to have AVN of her right knee in April 2018, with replacement in October of the same year. The patient also developed AVN of the right distal tibia in March 2019 (Figure 1) and underwent open-reduction internal fixation of a tibial fracture due to AVN in April 2019. Figure 1 demonstrates increased T2 hyperintensity on MRI imaging of the right tibia, indicative of AVN. Other causes of nontraumatic AVN, including alcoholism and hematological diseases, were excluded for this patient.

In August 2019, after years of stable brain MRI findings, the patient's neuro-oncologist became concerned for disease progression based on clinical and radiographic changes. The patient developed symptoms of worsening headaches with increasing frequency, in addition to T2 fluid-attenuated inversion recovery (FLAIR) changes on MRI, resulting in referral to neurosurgery for biopsy. The biopsy results demonstrated WHO grade 2, *IDH1*-mutant diffuse astrocytoma and the patient was initiated on metronomic temozolomide therapy in September 2019. The patient continued to have progressive headache symptoms and increased radiological findings, and a repeat biopsy in February 2020 demonstrated transformation to WHO grade 3 astrocytoma. At that time, she was initiated on concurrent radiation and temozolomide therapy and continued routine follow-up by neuro-oncology. The patient has not received steroids since December 2015 and is now limited in symptomatic management of her high-grade astrocytoma, as well as restricted from routine management of postsurgical resection with corticosteroids to prevent edema.

Upon further workup, the patient was found to have numerous endocrine complications, though only one pre-dates the diagnosis of low-grade astrocytoma and steroid use. She had undergone early menopause at 38 years of

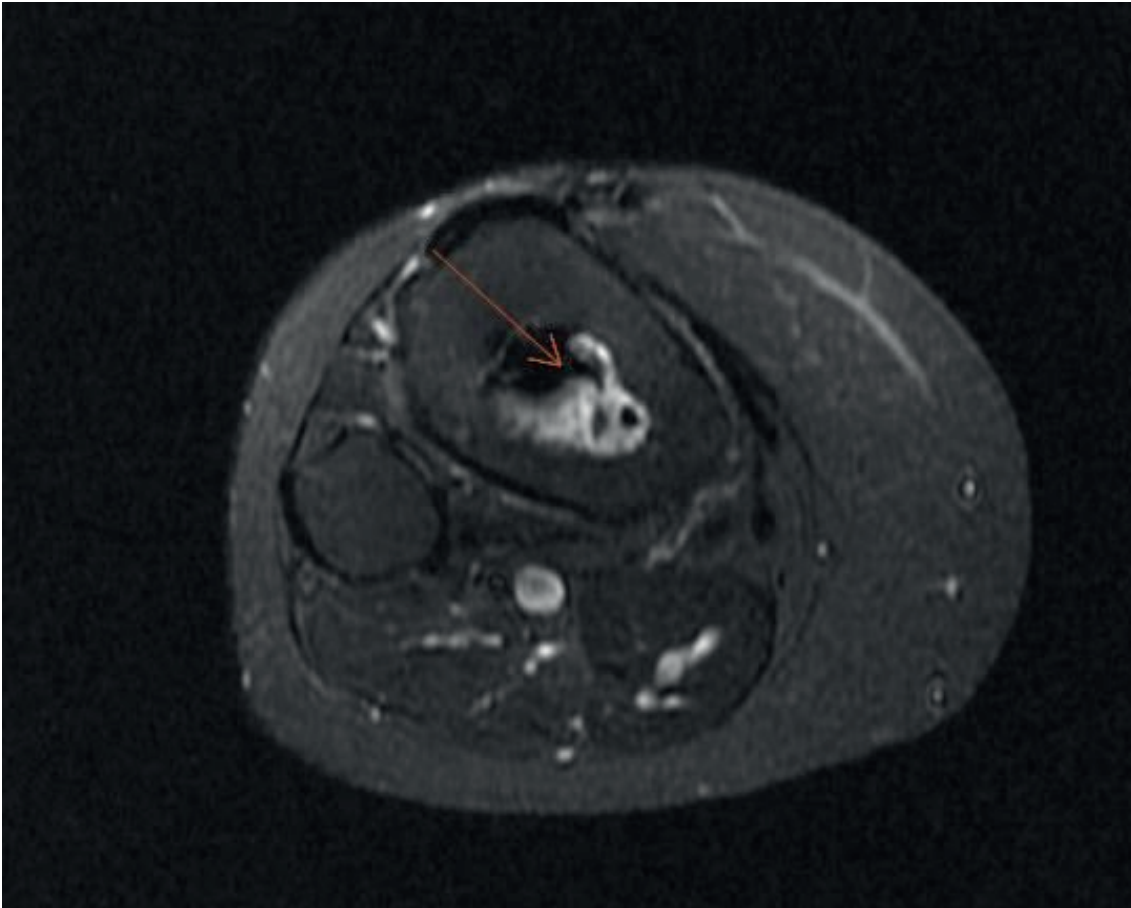


Figure 1. Avascular necrosis of the right tibia. T2 MRI imaging shows increased T2 hyperintensity as indicated by the arrow.

age, developed adrenal insufficiency (diagnosed in May 2016), had benign thyroid nodules identified in 2018 and developed diabetes insipidus in December 2019, just months after initiating temozolomide therapy. These multiple endocrine diagnoses further complicate the case and the multitude of clinical complications she has experienced in her treatment course.

Discussion

This case report presents a young, female patient with an astrocytoma who developed steroid-induced MJAVN after a short course of low doses of corticosteroids. AVN is typically associated with long courses and/or high doses of corticosteroids [10]. Our patient presented with joint pain that was eventually found to be MJAVN.

Corticosteroids are commonly used in the treatment of patients with brain tumors, particularly for the management of symptoms associated with edema [4]. Long-term and/or high-dose corticosteroid use can result in numerous short-term toxicities and, less frequently, long-term complications [3]. The overall incidence of steroid-induced AVN is not well established, though this complication is thought to be relatively rare [3]. The multitude of possible adverse events demonstrates the necessity of utilizing the shortest duration and lowest possible doses of steroids for symptomatic management.

Although steroid-induced AVN itself is thought to be rare, the involvement of multiple joints is highly uncommon. There are, however, a limited number of reports of MJAVN after corticosteroids, though all three patients reported had received high-dose corticosteroids; these patients received at least 100 mg of dexamethasone in total, with a mean exposure to 300 mg of dexamethasone [13]. The patient presented in the current report is unique due to the multi-joint involvement of AVN following a short course of low-dose corticosteroids. This case illustrates

Table 1. Steroid-related complications experienced by patient.

Acute complications	Chronic complications
<ul style="list-style-type: none"> • Increased appetite • Weight gain • Irritability • Mania 	<ul style="list-style-type: none"> • Adrenal insufficiency • Multi-joint avascular necrosis (bilateral hips and knees, right tibia)

that a low threshold for imaging should be maintained for patients with primary brain tumors or brain metastases who have had exposure to steroids at any dosage and who present with joint pain.

Endocrine complications have also been associated with the development of AVN, most notably panhypopituitarism [14]. The use of corticosteroids may contribute to endocrine complications such as adrenal insufficiency [3]. The patient in this report had numerous endocrine findings that were identified during the course of her workup for astrocytoma and subsequent AVN (Table 1). Further, although no formal endocrine diagnoses had been made prior to the astrocytoma diagnosis, the young age at which she underwent menopause could suggest underlying endocrine complications that were pre-existing.

Future perspective

This case highlights the importance of early intervention and assessment of joint pain in patients with brain tumors who have been exposed to corticosteroids. We also hope to convey that while corticosteroids are a mainstay in the symptomatic treatment of brain tumors, they are not benign in their potential for short-term and long-term complications for these patients.

Author contributions

All authors contributed to the study conception, design and writing of the manuscript. All authors contributed to the final manuscript.

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Ethical conduct of research

Informed consent was obtained for this case report.

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References

- Ostrom QT, Cioffi G, Gittleman H *et al*. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro Oncol*. 21(Suppl. 5), v1–v100 (2019).
- Perkins A, Liu G. Primary brain tumors in adults: diagnosis and treatment. *Am. Fam. Physician* 93(3), 211–217 (2016).
- Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: benefits and pitfalls. *Expert Rev. Clin. Pharmacol*. 4(2), 233–242 (2011).
- Galicich JH, French LA, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. *J. Lancet* 81, 46–53 (1961).
- Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: an update. *Neurooncol. Pract.* 2(1), 6–12 (2015).
- Roth P, Wick W, Weller M. Steroids in neurooncology: actions, indications, side-effects. *Curr. Opin. Neurol.* 23(6), 597–602 (2010).
- Ryken TC, McDermott M, Robinson PD *et al*. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* 96(1), 103–114 (2010).
- Sturdza A, Millar BA, Bana N *et al*. The use and toxicity of steroids in the management of patients with brain metastases. *Support. Care Cancer* 16(9), 1041–1048 (2008).

9. Arvold ND, Armstrong TS, Warren KE *et al*. Corticosteroid use endpoints in neuro-oncology: Response Assessment in Neuro-Oncology Working Group. *Neuro Oncol.* 20(7), 897–906 (2018).
10. Nakamura J, Ohtori S, Sakamoto M, Chuma A, Abe I, Shimizu K. Development of new osteonecrosis in systemic lupus erythematosus patients in association with long-term corticosteroid therapy after disease recurrence. *Clin. Exp. Rheumatol.* 28(1), 13–18 (2010).
11. Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open. Orthop. J.* 6, 449–457 (2012).
12. Baig SA, Baig MN. Osteonecrosis of the femoral head: etiology, investigations, and management. *Cureus* 10(8), e3171 (2018).
13. Taylor LJ. Multifocal avascular necrosis after short-term high-dose steroid therapy. A report of three cases. *J. Bone Joint Surg. Br.* 66(3), 431–433 (1984).
14. Uppal J, Burbridge B, Arnason T. Bilateral osteonecrosis of the hip in panhypopituitarism. *BMJ Case Rep.* 12(2), e227471 (2019).