CASE REPORT

Bevacizumab-associated osteonecrosis of the femur and tibia

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Abstract

Osteonecrosis is a multifactorial process that can affect different skeletal structures of the body. Osteonecrosis of the jaw associated with bevacizumab, steroids and bisphosphonates, alone or in combination, is a well-documented phenomenon. There are few cases of involvement of the appendicular skeleton. Magnetic resonance imaging is the most sensitive method for diagnosis. We hereby report two cases of osteonecrosis in the right tibia and in bilateral femoral heads in patients with adenocarcinoma of the lung and ovarian papillary serous carcinoma, respectively, that developed the complication after long-term bevacizumab exposure. Long-term exposure to antiangiogenic treatment may be a potential risk factor. Oncologists should be aware that osteonecrosis is a rare but real toxicity associated with bevacizumab and other antiangiogenics, which can occur in locations different from the jaw.

INTRODUCTION

Angiogenesis is a key mechanism in cancer development and survival by which tumors can develop new blood vessels, augmenting their vasculature apparatus [1]. It is mediated by many complex molecular pathways, including those involving participation of the signal proteins of the vascular endothelial growth factor (VEGF) subfamily. Bevacizumab is a humanized monoclonal immunoglobulin G1 antibody against all human VEGF isoforms and has been studied in oncology since its development in 1997 [1]. Food and Drug Administration approved bevacizumab for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, metastatic cervical cancer and advanced ovarian cancer. Due to possible changes in vasculature patterns and blood flow, some of the more usual bevacizumab adverse effects tend to be hypertension, proteinuria and wound-healing complications after surgery.

Osteonecrosis arises from the interruption of bone vascular circulation by a local trauma or by a non-traumatic factor, and subsequent cellular death and possible fractures [1,2]. Its precise pathogenesis has yet to be elucidated, but it appears to be the result of the combined effects of genetic predisposition, metabolic factors and local factors, such as vascular damage, increased intraosseous pressure and mechanical stresses. This pathological entity has been related to multiple causes, and many risk factors (e.g. alcohol, corticosteroid therapy, bisphosphonates, hemoglobinopathies, local radiotherapy or surgery) have been reported throughout the years [1,3]. The incidence of osteonecrosis is not fully established, but data for femoral head involvement estimate 20 000 to 30 000 new cases annually in the United States [4].
We hereby report two cases of osteonecrosis in the right tibia and in bilateral femoral heads in patients with adenocarcinoma of the lung and ovarian papillary serous carcinoma, respectively, that developed the complication after long-term bevacizumab exposure.

**CASE REPORT 1**

Patient 1 was a 39-year-old woman with no smoking history who was diagnosed with locally advanced adenocarcinoma of the lung at age 34. She was first treated with standard chemoradiation with curative intent but presented with brain metastases after a 1-year follow-up. Biopsy and molecular assessment of the metastases revealed an EGFR exon 20 insertion in tumor cells DNA. The patient was then started on afatinib, remaining on treatment for 23 months until the patient developed systemic progression of disease, along with new cerebral lesions. Stereotactic radiotherapy of the brain lesions was performed and a combination of carboplatin, pemetrexed and bevacizumab (7.5 mg/kg) was started. After six cycles of therapy, the carboplatin was discontinued and maintenance doses of pemetrexed and bevacizumab (7.5 mg/kg) were administered, for a total of 13 courses. At this point, the patient started to complain of severe pain in the right leg. The patient had no prior history of trauma or bisphosphonate use, and no evidence of bone metastases at the time. Radiologic assessment of the leg revealed an aspect consistent with osteonecrosis of the right tibia with incomplete fracture (Fig. 1) and osteonecrosis of the distal ipsilateral femur (Fig. 2). Bevacizumab was discontinued and the patient underwent surgical fixation of the fracture with improvement of the symptoms in the subsequent weeks.

**CASE REPORT 2**

Patient 2 was a 60-year-old woman with a smoking history who had been diagnosed with serous papillary adenocarcinoma of the ovary at age 37 and underwent surgical treatment at the time. Almost 15 years later, she had a recurrence in the mediastinum and was treated with six courses of carboplatin and paclitaxel, followed by daily anastrozole and subsequently tamoxifen. After 22 months of hormone therapy, she had disease progression exclusively in the lymph nodes and underwent surgical resection of the nodes and six courses of chemotherapy with carboplatin and gemcitabine associated with bevacizumab (7.5 mg/kg), at which point the chemotherapy was discontinued and the antiangiogenic therapy maintained. After receiving 10 additional cycles of bevacizumab, the patient started to complain of bilateral pain in the coxofemoral joints. A magnetic resonance imaging of the hips revealed bilateral osteonecrosis of the femoral heads with more severe involvement of the left
Table 1: Patient’s characteristics

| References          | Sex | Age | Primary tumor or pathology               | Metastatic sites | Antiangiogenic agent | Concomitant bisphosphonates | Duration of therapy (months) | Osteonecrosis                  |
|---------------------|-----|-----|------------------------------------------|------------------|----------------------|-----------------------------|-----------------------------|-------------------------------|
| Guillet et al., 2010 | M   | 53  | Hepatocellular carcinoma                 | Bone, lymph node | Sorafenib            | No                          | 10                          | Bilateral femoral heads       |
| Mir et al., 2011    | M   | 62  | Colon adenocarcinoma                     | Liver, lung      | Bevacizumab          | No                          | 5                           | Left femoral head             |
| Mir et al., 2011    | M   | Unknown | Renal cell carcinoma                  | Bone             | Sunitinib            | No                          | 4.3                         | Bilateral femoral heads       |
| Mir et al., 2011    | M   | 64  | Rectal adenocarcinoma                    | Liver, lung      | Bevacizumab          | No                          | 4.5                         | Left femoral head             |
| Koczywas and Cristea, 2011 | F | 43  | Lung adenocarcinoma                      | Liver, brain     | Bevacizumab          | No                          | 12                          | Right humeral head            |
| Tabouret et al., 2015 | F | 72  | Colon adenocarcinoma                     | Lung, brain      | Bevacizumab          | No                          | 39 (8 doses)                | Bilateral osteonecrosis in the knees |
| Steineger et al., 2018 | M | 66  | Hereditary hemorrhagic telangiectasia   | None             | Intranasal bevacizumab | No                      | 20                          | Right distal femoral and right tibia |
| Current             | F   | 39  | Lung adenocarcinoma                      | Brain, lymph node| Bevacizumab          | No                          | 12                          | Bilateral femoral heads       |
| Current             | F   | 60  | Serous papillary adenocarcinoma ovarv   | Lymph node       | Bevacizumab          | No                          | 12                          | Bilateral femoral heads       |

side, which led to discontinuation of bevacizumab (Fig. 3). The patient had no history of local trauma or concomitant use of bisphosphonates. Arthroplasty on the left hip joint was performed, and the pathology review showed evidence of bone necrosis, fibrovascular tissue with congestion and fibrosis, but no signs of malignant cells and was later submitted to the same procedure on the right side. The patient experienced complete resolution of the symptoms after surgeries.

**DISCUSSION**

The association between antiangiogenics and osteonecrosis has been noted in many clinical trials, and the jaw seems to be the classical site of involvement, especially when this drug class is used concurrently with bisphosphonates or corticosteroids [3, 4]. Involvement of the appendicular skeleton appears to be even more uncommon, with only seven cases in adults (Table 1) reported so far, to the best of our knowledge [1, 2, 5, 7, 8]. One of the cases refers to osteonecrosis after intranasal injection with bevacizumab in treating hereditary hemorrhagic telangiectasia [6]. A potential negative influence of bevacizumab on the incidence and severity of osteonecrosis of the jaw has been suggested in patients receiving zoledronic acid [9].

Magnetic resonance imaging is the most sensitive method for diagnosis, being of particular importance for being able to evidence changes early in the course of disease. The earliest finding is normally a single-density line (low-intensity signal) that represents the separation of normal and ischemic bone, on T1-weighted images. A second high-intensity line appears on T2-weighted images, which is the pathognomonic double-line sign, representing hypervascular granulation tissue [10].

Long-term exposure to antiangiogenic treatment may induce a chronic local ischemia that manifests with multiple clinical presentations. Some reports identified the potential risk of long-term exposure to antiangiogenic therapy for osteonecrosis induced by bevacizumab [2].

Oncologists should be aware that osteonecrosis is a rare but real toxicity associated with bevacizumab and other antiangiogenics, which can occur in locations different from the jaw. The joint or bone pain in patients receiving anti-VEGF therapy can be related to treatment complications and should be screened for osteonecrosis. An early diagnosis enables bevacizumab discontinuation before symptoms become chronic and/or irreversible, and prompt therapeutic intervention can be beneficial.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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**CONSENT**

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

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