CASE REPORT

Osteonecrosis of the mandible in a patient with lung adenocarcinoma undergoing anti-angiogenic therapy with bevacizumab

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Abstract

Bevacizumab is a recombinant monoclonal humanised antibody, designed to inhibit the binding ability of vascular endothelial growth factor to its receptor. Recently bevacizumab has been implemented in the treatment protocols against certain types of cancer. A 63-year-old Caucasian male patient with lung adenocarcinoma, presented in the OMFS clinic with a non-healing lesion of the mucosa at the region of tooth 17 including areas of exposed bone and presence of pus along with paraesthesia, distributed to the left side of the lower lip. The patient had undergone two chemotherapy cycles including IV bevacizumab which was administered once every 3 weeks in a dose of 15 mg/kg. The radiographic examination (Orthopantomogram, ConeBeamComputedTomography) revealed cortical erosion of the lingual plate on the posterior left mandibular region with involvement of the inferior alveolar nerve. A diagnosis of stage II osteonecrosis was established that was later confirmed by the histopathological evaluation and ruled out possible bone metastases. After 2 weeks of treatment with an empiric antibiotic regimen, the necrotic lesion was removed with surgical debridement and without complications. In the 6 months follow-up the diseased area was fully healed and the paraesthesia was improved.

Clinical relevance

Osteonecrosis of the jaw is a rare implication of angiogenic therapy with bevacizumab and only a few case reports have been published on the matter. The data from the present report further contributes to the understanding of the disease’s pathophysiology and to the foreground for the publication of official guidelines regarding the management of patients receiving antiangiogenic treatment.

Introduction

Bevacizumab is a recombinant humanised monoclonal antibody that targets the vascular endothelial growth factor A (VEGF-A) and inhibits the ability of VEGF to bind on its receptor⁴. The FDA has approved the use of bevacizumab for the treatment of metastatic colorectal cancer, advanced non-squamous non-small cell lung cancer, metastatic renal cell carcinoma and glioblastoma.

A series of case reports have been published recently, relating the use of this monoclonal antibody with osteonecrosis of the jaw (Table 1), while a strong association between bisphosphonates and the disease has already been established¹¹. Medication related ONJ, is the pathological clinical entity, that is recorded in patients who have not been radiated for therapeutic purposes and exposed bone has been revealed in the maxillofacial region or can be probed through fistula(e), persisting at least for 8 weeks, after current or previous use of antiresorptive or antiangiogenic agents¹¹. In 2008 it was first reported by Estilo et al., that a 51- and a 33-year-old female patients, who were
Table 1  No bisphosphonates were administered in the following case reports. Patients received bevacizumab intravenously.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Affected Jaw</th>
<th>Oral risk factors¹</th>
<th>Type of treatment</th>
<th>Comments/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estilo CL et al., 2008²</td>
<td>51</td>
<td>F</td>
<td>ductal carcinoma of right breast</td>
<td>mandible</td>
<td>none</td>
<td>Bone filing, chlorhexidine 0,12%</td>
<td>bev causative factor of ONJ/ clinicians should be aware</td>
</tr>
<tr>
<td>Estilo CL et al., 2008²</td>
<td>33</td>
<td>F</td>
<td>glioblastoma multiforme</td>
<td>mandible</td>
<td>none</td>
<td>disease self-limited</td>
<td></td>
</tr>
<tr>
<td>Greuter S et al., 2008¹</td>
<td>63</td>
<td>F</td>
<td>local relapse of breast cancer</td>
<td>maxilla</td>
<td>25,26 extracted</td>
<td>jaw extripation, sinus drainage</td>
<td></td>
</tr>
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<td>Greuter S et al., 2008¹</td>
<td>33</td>
<td>F</td>
<td>glioblastoma multiforme</td>
<td>mandible</td>
<td>none</td>
<td>disease self-limited</td>
<td></td>
</tr>
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<td>Greuter S et al., 2008¹</td>
<td>63</td>
<td>F</td>
<td>local relapse of breast cancer</td>
<td>maxilla</td>
<td>25,26 extracted</td>
<td>jaw extripation, sinus drainage</td>
<td></td>
</tr>
<tr>
<td>Serra E et al., 2009⁰</td>
<td>N/A</td>
<td>M</td>
<td>lung adenocarcinoma/bone metastases</td>
<td>mandible</td>
<td>dental extraction</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Bettini Get al., 2012²</td>
<td>N/A</td>
<td>F</td>
<td>non-small-cell lung cancer</td>
<td>mandible</td>
<td>N/A</td>
<td>disease self-limited</td>
<td></td>
</tr>
<tr>
<td>Brunamonti B et al., 2012²</td>
<td>47</td>
<td>M</td>
<td>Primitive adenocarcinoma of parotid gland</td>
<td>mandible</td>
<td>Eruption of third molar</td>
<td>N/A</td>
<td>clinicians should be aware of ONJ/bev relation. bev patients need appropriate dental management.</td>
</tr>
<tr>
<td>Pakosch Det al., 2011²</td>
<td>53</td>
<td>F</td>
<td>pancreatic carcinoma</td>
<td>mandible</td>
<td>Lower denture</td>
<td>decortication, local debridement, solcoseryl cream</td>
<td></td>
</tr>
<tr>
<td>Dişel Uet al., 2012²</td>
<td>51</td>
<td>M</td>
<td>Metastatic carcinoma of sigmoid colon</td>
<td>mandible</td>
<td>N/A</td>
<td>curettage</td>
<td></td>
</tr>
<tr>
<td>Sato Met al., 2013³</td>
<td>67</td>
<td>M</td>
<td>Sigmoid colon cancer peritonitis carcinomatosa</td>
<td>N/A</td>
<td>N/A</td>
<td>removal of necrotic tissue, bevacizumab break</td>
<td>bev could cause ONJ/dental exam. prior to treatment is needed</td>
</tr>
<tr>
<td>Santos-Silva AR et al., 2013²</td>
<td>61</td>
<td>M</td>
<td>clear cell/metastatic renal cell carcinoma</td>
<td>mandible</td>
<td>none</td>
<td>chlorhexidine 0,12%, bevacizumab and temsirolimus break</td>
<td>clinicians should be aware of potential ONJ in bev treatment</td>
</tr>
<tr>
<td>Current report</td>
<td>69</td>
<td>M</td>
<td>Lung adenocarcinoma</td>
<td>mandible</td>
<td>complete dentures</td>
<td>Antibiotics, sequestrectomy and removal of granulation tissue</td>
<td></td>
</tr>
</tbody>
</table>

¹Oral risk factors = dental extractions, dental prostheses, oral trauma.
receiving bevacizumab for recurring breast cancer and glioblastoma multiforme, respectively, developed osteonecrosis of the jaw (ONJ)\(^3\). Since that report\(^3\), bevacizumab has been considered as a potential causative factor of ONJ.

The present report aims to further raise the awareness of dental professionals about the relation between long-term administration of bevacizumab for oncology patients and ONJ and enrich the current knowledge by presenting the data from the following case of a bevacizumab associated osteonecrosis of the mandible in a cancer patient with lung adenocarcinoma.

**Case report**

A 69-year-old Caucasian male was referred to the OMFS clinic of Dental School of Athens, complaining of a non-healing lesion, with pus discharge, in the area of the left lower third molar and paraesthesia at the distribution of the left inferior alveolar nerve. The patient’s medical history was significant for lung adenocarcinoma which was diagnosed in 2009 for which he had undergone two cycles of chemotherapy (for 4 months in 2009 and during October 2012–January 2013). The therapeutic protocol of the chemotherapy included carboplatin, docetaxel and bevacizumab. The bevacizumab was administered every 3 weeks, in a dose of 15 mg/kg of body weight as an IV infusion. During the chemotherapy treatment the patient was also receiving 4 mg of cortisone p.o. on a daily basis. No surgical treatment or radiotherapy was required. No systemic diseases or allergies were reported.

After the end of the second cycle, the patient continued to receive bevacizumab, as a maintenance treatment and after 3 months noticed discomfort and pain at the left posterior area of the mandible along with progressing paraesthesia at the distribution of the inferior alveolar nerve. In a scale of 1 to 10 with 10 corresponding to a state of complete numbness and 1 to a natural state, the patient described the level of paraesthesia as 5 to 6. Intraoral examination revealed a 1 cm × 1.5 cm ulceration of the mucosa at the region of 17 with areas of exposed yellowish hard bone and presence of pus (Fig. 1). Extraoral examination did not reveal any pathological findings. Patient had been wearing a set of full dentures, for years which needed relining and denied any recent dentoalveolar surgery in the area.

The patient was referred for an Orthopantomograph (OPG) and a cone beam computed tomography (CBCT) of the mandible for further imaging investigation. The OPG revealed a radiolucent lesion at the left angle of the mandible with possible involvement of the inferior alveolar nerve (Fig. 2). The axial CBCT showed a radiolucent lesion with cortical erosion of the lingual plate on the posterior left mandibular region and involvement of the left trigeminal nerve (Fig. 3). According to the AAOMS\(^1\) classification, a diagnosis of stage II osteonecrosis of the mandible was established and surgical debridement of the area with perioperative antibiotic therapy was decided. The treatment with bevacizumab had been discontinued approximately 5 weeks before the surgery.

Prior to the operation, the patient had been receiving metronidazole 500 mg p.o. every 8 h, amoxicillin 500 mg p.o. every 6 h and chlorhexidine 0.12% mouthwash twice a day, for 2 weeks. Under local anaesthesia (xylocaine 2% with 1:100 000 epinephrine), a full-thickness envelope mucoperiosteal flap, with a length of 3 cm, was developed at the area of the lesion. All the sequestrums, along with the surrounding granulation tissue were removed, fixed in 10% buffered formalin and submitted for microscopic examination, in order to rule out bone metastases. The surgical wound was irrigated with normal saline and sutured with absorbable Vicryl™ 3:0 sutures. The usual
postoperative instructions were given to the patient with special attention to the good oral hygiene and the same antibiotic regimen was prescribed for 2 more weeks. The patient was also advised to have his complete dentures relined, with a tissue conditioner, in order to avoid any further intraoral trauma. The postoperative course was uneventful and 8 weeks after the surgery complete healing of the area was observed but the paraesthesia of the lower left lip remained.

As regards the histopathological analysis, grossly, both soft and hard tissue specimens were received, totaling approximately 2 cm. The hard tissue specimens were decalcified in Osteodec® (Bio Optica, Milano, Italy) for 4 days. Microscopic examination of 5 μm thick paraffin embedded tissue sections showed that the soft tissue specimens were composed of cellular and vascular fibrous connective tissue, heavily infiltrated by inflammatory cells, mostly lymphoplasmacytes and polymorphonuclear, and were covered by parakeratinised squamous epithelium. The hard tissue specimens consisted of bone trabeculae that showed empty lacunae, no osteoblastic or osteoclastic rimming, and many microbial colonies, both on their surface and bone marrow spaces. The microscopic findings were consistent with ONJ.

At the 6 months follow-up appointment, there were no signs of recurrence of osteonecrosis and the paraesthesia was improved with patient describing the level of paraesthesia as 3 to 4.

**Discussion**

**Medication related osteonecrosis of the jaw**

Medication related ONJ has been associated with the use of antiresorptive or antiangiogenic agents. Apart from the bisphosphonates, denosumab is an antiresorptive agent which acts as a RANK L inhibitor and has been correlated with a similar risk of ONJ induction in patients undergoing cancer treatment as in patients receiving zoledronate. Zoledronate has been reported to inhibit angiogenesis which is one of the major hypotheses of ONJ induction and recently the antiangiogenic agents, sunitinib, sorafenib, bevacizumab and sirolimus have been recognised as possible ONJ triggering factors. However, denosumab does not have antiangiogenic properties.

**The role of bevacizumab in ONJ induction**

Bevacizumab mainly inhibits the VEGF binding ability on the protein tyrosine kinases receptors, VEGFR-1 and VEGFR-2, and as a result deactivates this angiogenic pathway. Being one of the prime promoters of new blood vessel formation, the VEGF induces mitosis to endothelial cells, mostly lymphoplasmacytes and polymorphonuclear, and increases microvascular permeability. Depending on the local microenvironment and via the up-regulation of VEGF by the tumour cells, when a microtumour reaches a critical number of cells (from 50–100 to 1M cells) the higher energy demands that occur, will lead to the induction of a micro-vascular network, which will provide these cells with the appropriate oxygen supply. Consequently, by interfering the VEGF’s signaling pathway with the use of monoclonal antibodies, these energy demands cannot be supplied and the tumour cells number decrease, along with their ability to proliferate and metastasise.

However, this is not the only effect resulting by its pharmacological action. T cells transmigration and localisation on inflammation sites have been associated with increased levels of VEGF. The inhibition of KDR (VEGF receptor 2 on T-cells) – VEGF interaction either by an anti-KDR or an anti-VEGF (bevacizumab) antibody lead to a decreased number of transmigrated T-cells and concomitantly reduced the rate of this procedure. This protein also seems to play a role in

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Figure 3 The axial CBCT also revealed possible infiltration of the left inferior alveolar nerve, indicated with the yellow arrows.
the differentiation of monocytes and macrophages along with their chemotaxis and chemokine production. Furthermore, through the interaction with VEGFR-1, migration of monocytes is induced, and transendothelial polymorphonuclear neutrophil migration is modulated and activated\textsuperscript{23,24}. Therefore, a decrease in VEGF’s effectiveness, due to an anti-angiogenic therapy, could result in a reduced host immune response, as well. The inhibition of both of these actions could have a take part in the pathophysiology ONJ.

**ONJ in patients treated with bevacizumab and bisphosphonates**

Bisphosphonates which are widely accepted as an ONJ inducing factor\textsuperscript{11}, also reduce the VEGF levels, though not on the same scale as bevacizumab\textsuperscript{25}. Moreover, concomitant use of bisphosphonates and bevacizumab has been associated with increased risk of ONJ\textsuperscript{26}.

**ONJ in patients treated with bevacizumab alone**

However, only a few cases have been published associating the use of bevacizumab with ONJ in cancer patients without a history of bisphosphonate treatment. In the first published report on the subject, by Estilo et al., a 51-year-old patient receiving a dose of 15 mg/kg of bevacizumab, every 3 weeks, complained of having a sense of protruding bone in the mandible after approximately 3½ months of the drug’s administration (Table 1). The patient continued the anti-angiogenic treatment and 2 months later she was diagnosed with osteonecrosis of the mandible\textsuperscript{3}. However, in the current report the patient was receiving the same anti-angiogenic dose but developed ONJ after 7 months of consecutive use of bevacizumab. In the report of Diegel et al., it was shown that the minimum recommended dose of bevacizumab (5 mg/kg once every 2 weeks), was also capable to induce ONJ in a 51-year-old male patient with metastatic carcinoma of sigmoid colon\textsuperscript{8}.

In the report of Greuter et al., a 63-year-old female patient with ONJ of the maxilla related to bevacizumab developed osteonecrosis after the extraction of the left second premolar and first molar\textsuperscript{4}. In the report of Pakosch et al., a 53-year-old female patient, wearing a complete mandibular removable denture, developed a persistent purulent swelling in the area of the left first molar, after 4 months of bevacizumab treatment\textsuperscript{2}. The histopathological findings were consistent with ONJ. In the current report, the patient did not have any recent dentoalveolar surgery in the diseased area but was using a set of removable complete dentures which needed relining. Both dental extractions and the use of removable dentures have been reported to affect the induction of medication related ONJ\textsuperscript{11,27}.

Considering that in the aforementioned reports, ONJ was triggered in the same jaw that patients were using a problematic dental prosthesis or in areas of recent dental extractions, signifies the need to clarify which is the appropriate treatment protocol that should be followed by the dental team. Dental prostheses which could traumatise mucosa might trigger ONJ induction in cancer patients receiving drugs related to the disease, therefore adjustment prior to initiation of treatment with bevacizumab, could be protective. As regards dentoalveolar surgery, Hompes and Ruers reported that in order to avoid wound healing complications, any surgical operation should be programmed 5 to 8 weeks after the last administration of bevacizumab which can then be restarted 4 weeks after surgery or when the wound will be completely healed\textsuperscript{28}. In the study of Sexton et al., regarding 62 cancer patients who were receiving bevacizumab, one female patient developed ONJ. The authors concluded that continuous oral examination is necessary for this category of patients in order to avert this adverse effect of bevacizumab\textsuperscript{29}.

**Conclusions**

As life quality of cancer patients is considerably affected by ONJ and the side effects of the disease, provision of any necessary dental treatment at the baseline followed by regular recalls could be a useful addition to the anti-angiogenic therapy curriculum that might prevent the induction of osteonecrosis. Therefore, the publication of official medical guidelines for the dental management of these patients is essential as would increase the awareness of clinicians and the comprehensiveness of relative treatment planning.

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**References**


