



Recurrent submandibular fistula after Sunitinib treatment in a patient with renal cell carcinoma: a case report

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Abstract

Sunitinib is commonly used in the treatment of patients with renal cell carcinoma and is associated with serious side-effects. We present the first report of a recurrent submandibular fistula in a patient treated with sunitinib. A 68-year-old man was referred to our clinic for a cutaneous fistula situated on the right side of his lower jaw. The patient had been diagnosed with bone metastases from a renal carcinoma 2 years ago and had received a single 4 mg dose of zoledronic acid and subsequent treatment with sunitinib 37.5 mg once daily for the past 4 weeks. The patient was treated surgically by a perilesional incision and primary closure with sutures, advised on meticulous oral hygiene and was kept on an antimicrobial agent in the form of clindamycin. After reinitiating his oncological treatment with sunitinib the cutaneous fistula re-appeared and bone abnormalities were also detected on his X-ray. After 18 months a contralateral cutaneous fistula was observed along with a spontaneous avulsion of the patient's left molar. Repeat surgical treatment and sequestrectomy was performed with the subsequent histopathological examination revealing a suspicion of osteonecrosis of the jaw and an associated Actinomyces infection.

Keywords: submandibular fistula, sunitinib, osteonecrosis of the jaw, renal cell carcinoma

Introduction

Sunitinib is a multi-targeted tyrosine kinase receptor inhibitor with a potent antitumor effect which is used as a second- or first-line chemotherapy agent in renal cell carcinoma (RCC). The drug inhibits the proliferation and limits the lifecycle of tumors expressing markers like vascular endothelial growth factor receptors (VEGFRs), Platelet-Derived Growth Factor Receptors (PDGFRs), Receptor Tyrosine Kinase, Receptor type Tyrosine Kinase 3, while also reducing angiogenesis via inhibition of VEGFRs and PDGFR- β expressed on endothelial cells and pericytes [1]. Side-effects of the drug include arterial hypertension, renal function deterioration with a decrease of the estimated glomerular filtration rate,

diarrhea, fatigue, skin rash, stomatitis, hand-foot syndrome and jaw osteonecrosis [2]. However, these are considered acceptable for the benefits provided by an oral chemotherapy agent. Sunitinib seems to increase oral toxicity, as compared with other chemotherapy drugs, with a significantly higher frequency of tooth color changes, pain, tooth mobility and gingival bleeding reported [3].

Osteonecrosis of the jaw (ONJ) is a bone degradation process which occurs as a result of the action of internal or external factors on bone tissue. A strong correlation between bone antiresorptive agents and the occurrence of maxillary osteonecrosis has been reported in the last two decades. A few different types have been described like bisphosphonate-related osteonecrosis

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of the jaw (BRONJ), denosumab related osteonecrosis of the jaw and antiresorptive osteonecrosis of the jaw. However, the latest definition provided by the American Association of Oral and Maxillofacial Surgeons groups all these types as medication related osteonecrosis of the jaw (MRONJ) [4]. The diagnosis of MRONJ require that all of the following characteristics are present: (1) Current or previous treatment with antiresorptive or antiangiogenic agents; (2) Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; (3) No history of radiation therapy to the jaws or obvious metastatic disease to the jaws [4]. Because of the antiangiogenic activity of Sunitinib which inhibits bone remodeling and delays the healing of soft tissue, it is considered as potentially enhancing the development of MRONJ [5].

Case report

A 68-year-old man complaining of local pain for the last 2 weeks was referred to our clinic with a submandibular fistula situated on the right side of his lower jaw, as seen in figure 1. On examination local inflammatory swelling, hyperemia, and bleeding were observed, but no pus or other signs of infection were observed.



Figure 1. Right sided submandibular fistula.

The initial suspicion was of poor dental status with periodontal disease as the cause of the fistula. This was evident in the patient's dental X-ray, as shown in figure 2.



Figure 2. Dental X-ray of the patient.

The patient had been diagnosed 2 years before with bone metastases of the right shoulder from a RCC metastasis with intense positive CD 10, intense positive CD 10 differentiates metastatic renal cell carcinoma (CD10+) from primary clear cell carcinoma (CD10-) [6] and negative S100, which excluded a possible secondary chondrosarcoma [7]. He received radiotherapy with an analgesic dose of 8 Gy and a single dose of zoledronic acid an intravenous bisphosphonate. Afterwards treatment with sunitinib was started with oral doses of 37.5 mg once daily for four consecutive weeks of therapy followed by 2 weeks of discontinuation. A CT scan performed one year later had described multiple bone metastases, but no pathological modification of the jaws. At that time the possibility of an early stage MRONJ was raised because of the history of zoledronic acid and sunitinib use. Antibiotic therapy with clindamycin 300 mg three times daily was started and a local cleaning with antiseptics was performed. Blood analysis revealed no signs of infection and bacteriological examination showed commensal flora.

Two days later, a perilesional incision was performed, followed by curettage (Figure 3) and primary closure with sutures. Post-operative wound appearance was satisfactory and apparent healing was obtained. Subsequently, the patient resumed chemotherapy with sunitinib with oral doses of 37.5 mg once daily for four consecutive weeks of therapy followed by 2 weeks of discontinuation and after a further two months of treatment the cutaneous fistula re-appeared in the same position (Figure 4).



Figure 3. Operatory view of the fistula.



Figure 4. Recurrence of the right-sided submandibular fistula.

Repeat dental X-ray revealed radiological signs of bone abnormalities with mandibular necrotic bone especially in the right lower side but also in the left mandibula, as shown in figure 5. One year after the first presentation spontaneous avulsion of a left molar was observed (Figure

6) and a decision to extract the right mandibular molars was taken (Figure 7).

After one and a half years the patient presented again with cutaneous mandibular fistula of the contralateral site and avulsion of upper second premolar (Figure 8).



Figure 5. Follow-up dental X-ray of the patient with observed bone abnormalities.

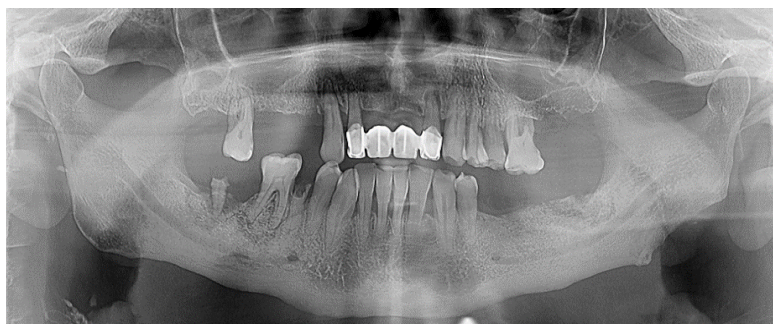


Figure 6. Follow-up dental X-ray of the patient after a spontaneous avulsion of the left molar.



Figure 7. Dental X-ray after extraction.

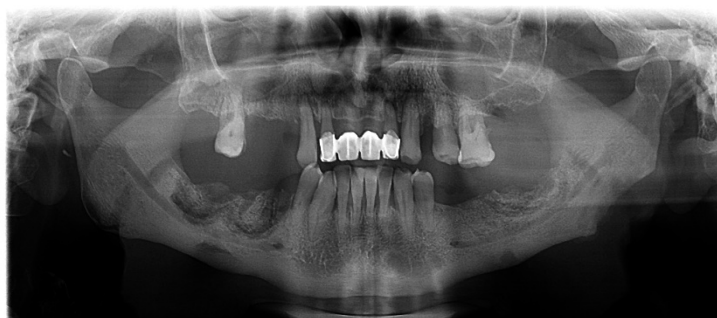


Figure 8. Bilateral mandibular sequestrum, premolar avulsion.

The decision to perform surgery and sequestrectomy was taken. Using piezo surgery, for minimal invasive bone trauma, bilateral sequestrum was collected and closed with primary suture with nonresorbable suture. The subsequent histopathological examination revealed a suspicion of osteonecrosis of the jaw with an associated Actinomyces infection.

Discussion

Clinical trials have revealed the efficacy of sunitinib on RCC by inducing tumor necrosis and regression. Common side effects like arterial hypertension, gastrointestinal toxicity, diarrhea, fatigue, skin rash are sometimes associated with fatal outcomes, which have been previously reported, and osteonecrosis have also been mentioned [2,3,8]. Although sunitinib use is the probable cause, BRONJ may also be considered in this patient due to the single dose of zoledronic acid received [9,10]. The therapeutic effects of bisphosphonates on bone resorption have revolutionized the treatment of patients with bone damage. These drugs are also considered the golden standard of therapy for managing cancer related conditions, including metastases of solid tumors, such as prostate, breast and lung cancer. The side effects of bisphosphonate treatment have long been studied, but overall, the drugs have been well tolerated and only the occurrence of osteonecrosis of the jaw has diminished the prescribers' enthusiasm.

The influence of sunitinib on growth factor activity and revascularization makes its effects more likely to be incriminated in the appearance of the fistulas. Cases of MRONJ have been reported in patients who had previously received bone modifying or angiogenic inhibitor agents with no other history of head and neck irradiation. Evidence about the relationship between ONJ and new target therapies such as sunitinib is still limited, however such cases have been previously reported [5,11,12]. There are different opinions on the ideal management of MRONJ, although it seems that cessation of the drug improves the situation in all cases. Further evidence is needed in order to improve recommendations for treatment for such patients [5]. A possible synergistic effect of the concomitant use of sunitinib and bisphosphonates can also be incriminated [9].

Regarding the current case presentation, specifically the recurrent cutaneous fistula, the main issue raised by the case is if it can be considered a direct side effect of the sunitinib treatment, an infectious complication of a preexisting MRONJ with actinomyces, or a complication of periodontal disease and poor hygiene.

Another issue is the optimal time until surgery in such cases, which could be during the first stages of MRONJ or in the later stages, when radiological bone sequestrum appears [13-15].

Because MRONJ is a multifactorial condition, an etiological treatment cannot be pursued and, at the moment, consensus on the ideal treatment has not been achieved. Management efforts are aimed at slowing down or even stopping the progress of disease. It is also necessary to establish a dental protocol that is adapted to all patient situations according to basic pathology, antiresorptive treatment, the current status of the disease and MRONJ stage. A multidisciplinary approach is needed in the treatment of this condition in order to determine the appropriate timing of intervention, or perhaps even the creation of a biologically favorable window for the treatment of the complication achieved by a temporary interruption of the antiresorptive medication if considered appropriate [16-18].

Conclusion

Previous cases of ONJ after sunitinib treatment have been reported; this the first case of a recurrent submandibular fistula after sunitinib treatment in a patient with RCC, which represents an increased interest in this patient. This type of jaw side effect can influence the quality of life and outcomes of oncological patients and awareness of this complication is important in improving patient care.

Ethics approval

The study was approved by the Ethics Committee of County Emergency Clinical Hospital of Targu Mures Nr. Ad. 1171/18.01.2019.

Consent to participate

Written informed consent was obtained from the patient to publish this paper.

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