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ORIGINAL ARTICLE

Oral avascular bone necrosis associated with chemotherapy and biphosphonate therapy

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BACKGROUND: Oral avascular bone necrosis is an important adverse effect of chemotherapy and biphosphate therapy.
OBJECTIVE: To report our experience in oral avascular bone necrosis in cancer patients assigned to undergo chemotherapy.
PATIENTS AND METHODS: Fourteen patients presenting oral avascular bone necrosis were selected from the clinical files of five Stomatological Clinics in Brazil. Clinical data as well as treatment and prognosis information were obtained from all 14 patients.
RESULTS: Twelve patients (86%) were submitted to biphosphonate therapy. The most important symptom was pain, present in all cases, and the mandible was the most common involved site. Most patients (79%) had their conditions managed by antibiotic therapy and surgical debridation; however complete response was achieved in only three cases (21%).
CONCLUSION: Avascular bone necrosis is a serious oral side-effect of cancer chemotherapy, particularly in patients using biphosphonates, and antibiotic therapy and surgical debridation were not able to promote complete response in most cases.
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Keywords: chemotherapy; mouth; oral; bone; biphosphonates; avascular bone necrosis

Introduction

Cancer patients who have undergone chemotherapy and biphosphonate therapy can present avascular bone necrosis. Most cases are associated with treatment of cancers involving bone, such as multiple myeloma or metastatic cancers (such as breast carcinoma) (Marx, 2003; Migliorati, 2003; Ruggiero *et al*, 2004). Many drugs used in cancer treatment, including osteoclast-inhibiting drugs, have an anti-angiogenic potential, which is important for their anti-tumoral effects (Wood *et al*, 2002). On the other hand, inhibition of angiogenesis can predispose to the development of avascular necrosis. These drugs have been recently included in cancer treatment protocols and the number of reported cases of oral avascular necrosis is increasing. The aim of this study was to report 14 cases of oral avascular bone necrosis in cancer patients submitted to chemotherapy.

Patients and methods

The files of five Stomatological Clinics in Brazil (Estácio de Sá University Dental School; Hemocentro and School of Dentistry of Piracicaba, University of Campinas; and AC Camargo Cancer Hospital; private practice Stomatological Clinic) were reviewed for all cases of oral avascular bone necrosis in cancer patients who had undergone chemotherapy from January 2003 to May 2004. We considered the diagnosis of oral avascular bone necrosis by observing exposed necrotic bone, with or without pain and clinical signs of infection and acute inflammation, preceded by dental manipulation or not. We also excluded clinically, radiographically and histopathologically the possibility of metastatic disease, and other types of osteomyelitis. We included all patients diagnosed as having mandibular and/or maxillary avascular bone necrosis, not submitted to local radiotherapy, and previously submitted to chemotherapy. Clinical data as well as treatment, prognosis and follow-up information were obtained from all patients through careful examination and review of the clinical charts.

Results

Fourteen patients, all of them showing oral avascular bone necrosis, were included in the study. All patients were previously submitted to chemotherapy and 12

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(86%) were also under osteoclast-inhibiting drug regimens, including pamidronate and/or zolendronic acid. The 14 cases included: six patients with multiple myeloma, six patients with metastatic breast carcinomas, and one case each of metastatic prostate adenocarcinoma and metastatic lung adenocarcinoma. Avascular bone necrosis of the jaws occurred 5.9 years (range 2–12 years) after initial diagnosis of the cancer. All cases were observed in adults (mean age 63 years, range 43–84 years) and 10 cases (71%) affected female patients. Pain was reported by all patients and the mean reported time of bone exposure was 5 months (range 1 week to 24 months). Anemia, leucopenia and/or thrombocytopenia were present in nine patients (64%) on diagnosis of the oral avascular bone necrosis.

Clinical examination revealed necrotic bone exposure on the mandible (10 cases; 71%), maxilla (four cases; 29%) and hard palate (one case; 7%) (Figures 1–3). Mean area of bone exposure was 2.1 cm (range 0.5–5.0 cm). Nine cases (64%) were associated with previous dental manipulation before development of avascular necrosis. Case 5 showed a periapical radiolucent area associated to a lower molar and cases 3 and 6 presented severe periodontal disease in the affected area. Conservative measures were initially performed in all cases, including antibiotic therapy, improvement of local hygiene, 0.12% chlorhexidine rinses, and irrigation with a 10% hydrogen peroxide and 2% potassium iodine solution. Cases with persistent bone exposure were submitted to gentle surgical debridation (11 cases; 79%). We considered complete response in those cases where both pain and bone exposure were completely controlled, and partial response when only either pain control or reduction/absence of bone exposure were achieved. Seven patients (50%) reported no pain after treatment, but only three patients (21%) showed complete resolution of the exposed necrotic bone. Case 8 refused regular follow up and presented no clinical response. Table 1 shows a summary of the main clinical characteristics and treatment used in the 14 patients.

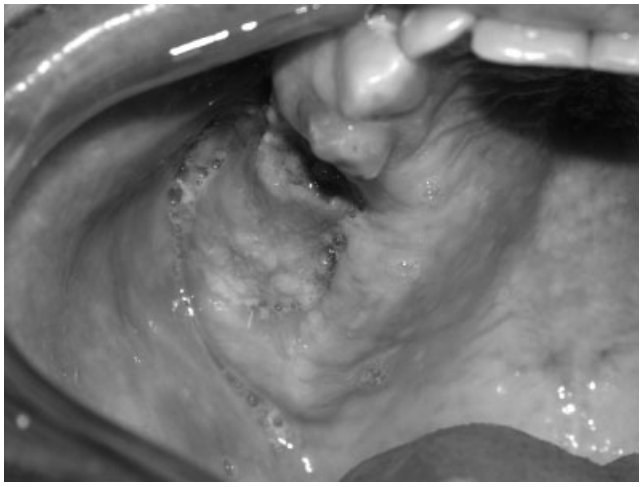

Figure 1 (Case 1) Large area of necrotic bone exposure on the right maxilla, 3 months after extraction of the upper right first premolar

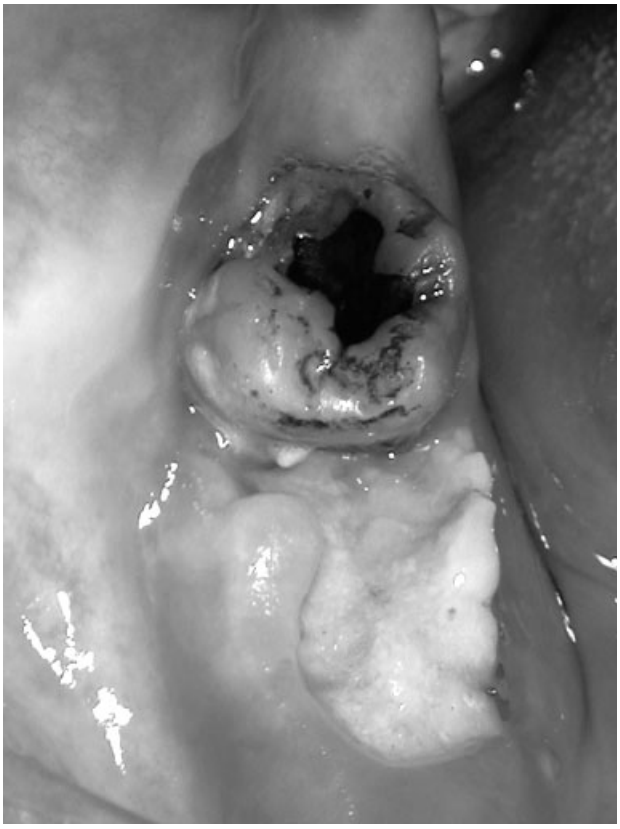

Figure 2 (Case 4) Detail of one area of necrotic bone exposure on the right posterior mandible following extraction of the lower right first molar

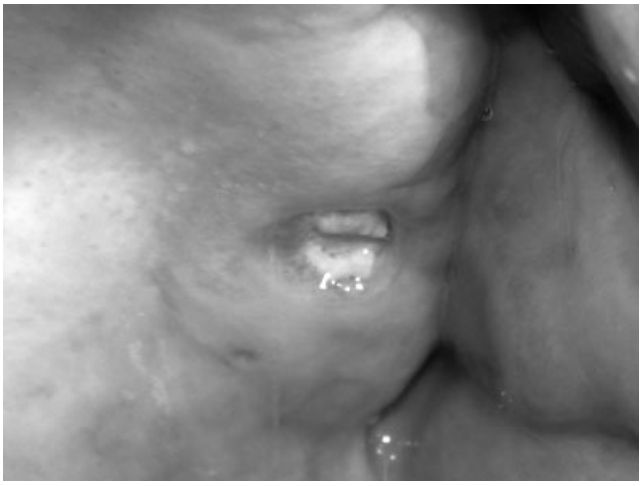

Figure 3 (Case 9) Small asymptomatic area of bone exposure on the left maxilla with previous history of extraction of the upper left first molar

Discussion

Recently, several reports have focused oral avascular bone necrosis in cancer patients, and biphosphonates, specially pamidronate and zolendronic acid, are considered the main etiologic agents for this process (Carter

Table 1 Base disease, clinical findings, treatment and course of 14 patients presenting oral avascular bone necrosis associated with cancer chemotherapy

	Clinical findings and base disease					*Oral necrosis*					
	Age (years)	*Sex*	*Disease*[a]	*Drugs*	*Laboratory findings*	*PDM*[b]	*Time*	*Site*	*Size (cm)*	*Tx*[c]	*Course*[d]
1	78	M	MM	Vincristine, zolendronic acid, pamidronate	Anemia leucopenia	Yes	2 months	Maxilla	3.0	ABT + Deb	PR painless
2	65	F	BC	Pamidronate, zolendronic acid, paclitaxel, docetaxel	Anemia thrombocytopenia	No	2 months	Mandible	1.0	ABT	PR painless
3	69	F	MM	Vincristine, dexamethasone	Anemia	No	6 months	Mandible	0.5	ABT + Deb	CR painless
4	84	F	MM	Thalidomide, pamidronate, dexamethasone	Anemia thrombocytopenia	No	1 month	Mandible	3.5	ABT + Deb	PR painless
5	53	F	MM	Vincristine, dexamethasone, thalidomide, pamidronate, cyclophosphamide	Anemia leucopenia	Yes	1 month	Mandible	3.0	ABT + Deb	PR
6	62	M	MM	Prednisone, dexamethasone, vincristine, pamidronate	Anemia, leucopenia, thrombocytopenia	Yes	1 month	Mandible	2.0	ABT	PR
7	74	M	MM	Thalidomide, prednisone	Normal	Yes	1 month	Maxilla	1.0	ABT + Deb	PR painless
8	68	F	BC	Zolendronic acid	Anemia thrombocytopenia	Yes	18 months	Mandible	1.0	ABT + Deb	NR
9	62	F	BC	Methotrexate, fluorouracil, pamidronate, zolendronic acid, doxetaxel, paclitaxel	Normal	Yes	2 months	Maxilla mandible	1.0, 1.0	ABT	PR
10	43	F	BC	Pamidronate	Anemia	Yes	24 months	Mandible	1.5	ABT + Deb	PR
11	47	F	Lad	Docetaxel, zolendronic acid	Leucopenia	No	1 week	Hard palate	1.0	ABT + Deb	PR
12	62	M	Pad	Pamidronate, zolendronic acid, docetaxel	Normal	Yes	9 months	Mandible	2.0	ABT + Deb	PR
13	46	F	BC	Pamidronate, zolendronic acid, paclitaxel	Normal	No	1 month	Mandible	1.5	ABT + Deb	CR painless
14	72	F	BC	Zolendronic acid, thalidomide	Normal	Yes	2 months	Maxilla (bilateral)	5.0, 1.5	ABT + Deb	CR painless

[a]MM, multiple myeloma; BC, breast carcinoma; Lad, lung adenocarcinoma; Pad, prostate adenocarcinoma.
[b]Previous dental manipulation.
[c]ABT, antibiotic therapy; Deb, surgical debridation.
[d]PR, partial response (absence of pain or reduction/absence of bone exposure); CR, complete response (absence of pain and absence of bone exposure); NR, no response.

and Goss, 2003; Marx, 2003; Migliorati, 2003; Estilo *et al*, 2004; Ruggiero *et al*, 2004). Apart from their main therapeutic effect as osteoclast inhibitors (Vitté *et al*, 1996), these drugs also have anti-angiogenic properties, such as decreasing levels of vascular endothelial growth factor (VEGF) (Coleman, 2000; Jantunen, 2002; Santini *et al*, 2002; Riccardi *et al*, 2003). Recently, Marx (2003), Migliorati (2003), Estilo *et al* (2004) and Ruggiero *et al* (2004) reported, respectively, 36, 5, 13 and 63 cases of oral bone exposure in patients treated with pamidronate and/or zolendronic acid. Similarly to our cases, other reports have shown that multiple myeloma and metastatic breast carcinoma are the most common base diseases associated with the use of these drugs and, consequently, to avascular bone necrosis (Marx, 2003; Pogrel, 2004; Ruggiero *et al*, 2004).

Some reports have demonstrated the anti-angiogenic effects of biphosphonates (Wood *et al*, 2002), and their capacity to predispose avascular bone necrosis. In addition, various other drugs for cancer therapy may, directly or indirectly, induce osteonecrosis and some of them are commonly used in association with biphosphonates (Tarassoff and Csermak, 2003; Ruggiero *et al*, 2004). Corticosteroids (dexamethasone and prednisone), thalidomide, vincristine, cyclosphosphamide, and methotrexate also have anti-angiogenic effects, such as inhibition of VEGF and basic fibroblast growth factor (Socie *et al*, 1994; Hui and Wiernik, 1996; Ayramis *et al*, 2001; Sung *et al*, 2002; Aricò *et al*, 2003; Wang *et al*, 2003). In addition, drugs used for treatment of glandular carcinomas, such as docetaxel and paclitaxel, would also impair normal healing and consequently predispose to osteonecrosis (Ayramis *et al*, 2001; Wang *et al*, 2003). In the series reported by Marx (2003), some patients had also received dexamethasone and were submitted to previous radiotherapy, and it is possible that these regimens would have also contributed to bone necrosis. In short series, such as the one reported here and most of the ones described in the literature, it is difficult to ascertain the individual importance of each drug or regimen.

In addition to the anti-angiogenic drug-induced effects, we should also consider blood cell count alterations and immunosuppression associated with the base disease and chemotherapeutic agents. Anemia, leucopenia, thrombocytopenia and immunosupression are common findings, and can lead to bone infection and necrosis. Nine of our 14 patients (64%) showed at least one of these alterations when presenting oral avascular bone necrosis.

Sung *et al* (2002) reported a case of maxillary osteonecrosis in an area previously affected by oral herpes simplex virus (HSV) lesions, and suggested that ulcerations associated with oral infections can lead to the breakdown of oral mucosal integrity, consequently increasing the risk of osteonecrosis in the affected area. None of our cases reported the presence of other previous oral lesions in the area, excepting periodontal disease and periapical inflammation.

Surgical debridation is useful on the management of these patients, and it is important to analyze all tissue removed from areas of avascular bone necrosis, to exclude the possibility of the presence of metastatic foci (Wang *et al*, 2003; Ruggiero *et al*, 2004). Conventional HE staining can be eventually complemented by immunohistochemistry when necessary, particularly in multiple myeloma, because of plasmacytic infiltrate, common in oral mucosal inflammation. This was performed in our case 1, and it was negative for cancer cells. All cases submitted to surgical debridation in our report revealed a histological picture compatible with osteomyelitis and necrotic bone, and in case 12 some bacterial colonies suggestive of actinomyces were also found.

Marx (2003) reported that 77% of their 36 patients presented avascular bone necrosis after tooth extraction, and only 23% had a spontaneous onset. Estilo *et al* (2004) reported nine cases (70%) after tooth extraction and 4 (30%) spontaneous cases, and Ruggiero *et al* (2004) reported only nine of 63 cases (14%) with spontaneous onset. This seems to be similar to what happens in osteoradionecrosis and reinforces the importance of the dental surgeon in preventing avascular bone necrosis during cancer therapy (Assael, 2004). Nine of our 14 patients (64%) had a previous history of surgical dental manipulation: teeth extraction in seven cases and periodontal surgery in two cases. In addition, similarly to other types of osteomyelitis, the mandible is the most common affected area, although the incidence of maxillary cases seems to be unexpectedly high (Estilo *et al*, 2004; Ruggiero *et al*, 2004). Antibiotic therapy, irrigation with 10% hydrogen peroxide associated with 2% potassium iodine, 0.12% chlorhexidine rinses, sequestrectomy and surgical debridation are the protocols in managing avascular bone necrosis (Estilo *et al*, 2004; Ruggiero *et al*, 2004). They are useful in controlling pain, the most common symptom, but have much less effect on necrotic bone exposure. These protocols did not promote complete clinical response in 11 of our cases (79%). We found a complete response in only three cases (cases 3, 13 and 14), and one of them (case 3) showed two peculiarities: the lesion was diagnosed and managed immediately after the beginning of bone exposure and the patient was not submitted to any osteoclast-inhibiting drugs. This reinforces that early diagnosis and prompt therapy are important for prognosis. Our cases also confirm that previous dental manipulation is not essential for development of avascular bone necrosis; however, it is expected that bone necrosis should be more common after dental procedures, in particular dental extractions.

Anti-angiogenic drugs are extremely important for cancer treatment, so the dental team must be prepared to deal with their possible oral side-effects. It is not possible to completely avoid surgical procedures in these patients, but rigorous protocols of dental hygiene and clinical follow-up will substantially decrease these interventions. It seems that, although biphosphonates seem to be relevant drugs in oral avascular bone necrosis, other anti-angiogenic drugs would also participate and, in addition, systemic effects of the base disease and chemotherapic effects should also be evaluated. It is

difficult to establish the individual importance of each variable, but several predisposing factors probably act concurrently in osteonecrosis. Oncologists should be aware of this serious and disabling oral side-effect of cancer treatment and oral support prior and during cancer therapy is essential in order to prevent and diagnose this condition, providing functional improvement and comfort to the patients.

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References

Aricò M, Boccalatte MFP, Silvestri D *et al* (2003). Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. *Haematologica* **88:** 747–753.

Assael LA (2004). New foundations in understanding osteonecrosis of the jaws. *J Oral Maxillofac Surg* **62:** 125–126.

Ayramis IA, Kwock R, Ayramis VI (2001). Taxotere and vincristine inhibit the secretion of the angiogenesis inducing vascular endothelial growth factor (VEGF) by wild-type and drug-resistant human leukemia T-cell lines. *Anticancer Res* **21:** 2281–2286.

Carter GD, Goss AN (2003). Biphosphonates and avascular necrosis of the jaws. *Aust Dent J* **48:** 268.

Coleman RE (2000). Optimising treatment of bone metastases by Aredia™ and Zometa™. *Breast Cancer* **7:** 361–369.

Estilo CL, Williams T, Evtimovska E *et al* (2004). Osteonecrosis of the maxilla and mandible: possible drug-induced complication of biphosphonate therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **97:** 449–450 (abstract).

Hui L, Wiernik PH (1996). Avascular necrosis of bone after adult acute lymphocytic leukemia treatment with methotrexate, vincristine, L-asparginase, and dexamethasone (MOAD). *Am J Hematol* **52:** 184–188.

Jantunen E (2002). Bisphosphonate therapy in multiple myeloma: past, present, future. *Eur J Haematol* **69:** 257–264.

Marx RE (2003). Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* **61:** 1115–1118.

Migliorati CA (2003). Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* **21:** 4253–4254.

Pogrel MA (2004). Biphosphonates and bone necrosis. *J Oral Maxillofac Surg* **62:** 391–392.

Riccardi A, Grasso D, Danova M (2003). Bisphosphonates in oncology: physiopathologic bases and clinical activity. *Tumori* **89:** 223–236.

Ruggiero SL, Mehrotra B, Rosenberg TJ *et al* (2004). Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* **62:** 527–534.

Santini D, Vincenzi B, Avvisati G *et al* (2002). Pamidronate induces modifications of circulating angiogenetic factors in cancer patients. *Clin Cancer Res* **8:** 1080–1084.

Socie G, Selimi F, Sedel L *et al* (1994). Avascular necrosis of bone after allogeneic bone marrow transplantation: clinical findings, incidence and risk factors. *Br J Haematol* **86:** 624–628.

Sung EC, Chan SM, Sakurai K *et al* (2002). Osteonecrosis of the maxilla as a complication to chemotherapy: a case report. *Spec Care Dent* **22:** 142–146.

Tarassoff P, Csermak K (2003). Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofac Surg* **61:** 1238–1239.

Vitté C, Fleisch H, Guenther H (1996). Bisphosphonates induces osteoblasts to secret an inhibitor of osteoclast-mediated resorption. *Endocrinology* **137:** 2324–2333.

Wang J, Goodger NM, Pogrel MA (2003). Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg* **61:** 1104–1107.

Wood J, Bonjean K, Ruetz S *et al* (2002). Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* **302:** 1055–1061.