Case Report

Skull base or cervical vertebral osteomyelitis following chemoradiotherapy for pharyngeal carcinoma: A serious but treatable complication

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Abstract

Osteomyelitis, infection of the bone and marrow, following high dose (chemo-)radiotherapy for head and neck cancer is uncommon and rarely seen in the cervical spine or temporal bone. Due to its proximity to critical structures, osteomyelitis in the latter regions could carry potentially important consequences. Furthermore, involvement near the skull base (e.g. temporal bone and high cervical vertebrae) presents unique challenges in diagnosis (especially in the differentiation from disease recurrence) and treatment, making early detection and timely intervention critical. In this report, we describe two cases of osteomyelitis, one involving the temporal bone and the other affecting the 2nd and 3rd cervical vertebrae (C2–C3), diagnosed and treated with good outcome in the setting of definitive chemoradiotherapy for locally advanced pharyngeal carcinomas. We suggest that for new or evolving post-radiotherapy osseous changes in regions that have received a high dose of radiotherapy, associated with unexpected and deteriorating spinal symptoms such as pain and spasm, radiation-related osteomyelitis should be considered in the differential diagnosis from tumor progression. Timely referral to a surgical oncologist and infectious diseases specialist is paramount in achieving satisfactory clinical outcomes.

Introduction

The treatment of locally advanced head and neck malignancies usually entails radical radiotherapy augmented by concurrent chemotherapy [1–4]. This approach permits organ preservation as an alternative to surgery in many advanced oropharyngeal cancers, or curative treatment for nasopharyngeal carcinoma where surgery is not ordinarily employed due to anatomic considerations. Unfortunately, the sequelae of radiation treatment often include stromal and vascular fibrosis with subsequent decreases in microcirculation [5]. The clinic-pathologic result of these changes may include delayed mucosal healing within the irradiated volume. In turn, persistent mucosal breakdown can serve as both a nidus and a portal of entry for infection due to loss of mucosal barrier function and compromised vascular supply [6].

Following active cancer treatment, patients generally undergo long-term surveillance. Post-radiotherapy radiographic changes in osseous and non-osseous tissues may occur for several reasons including radiotherapy-induced inflammation, fibrosis, osteonecrosis or disease recurrence. In this report, we present an additional entity that should be considered in the differential diagnoses of evolving symptomatic radiologic bone abnormalities. We describe two cases of osteomyelitis, one involving the temporal bone and the other affecting the 2nd and 3rd cervical vertebrae (C2–C3), diagnosed and treated with good outcome in the setting of definitive chemoradiotherapy (CRT) for locally advanced pharyngeal carcinomas.

Case 1

A 54-year-old male current smoker with a 40-pack year smoking history, peripheral vascular disease and polycythemia requir-
The anterior margin of the spinal cord [Fig. 2B–D].

cervical spine with development of an epidural collection abutting ulcerated area as well as increased marrow abnormalities in the performed after three months showed further progression of the ticemia or neurological compromise were evident. A repeat MRI revealed no evidence of malignancy. A bone scan showed no uptake in the cervical spine. MRI showed a slight increase in the extent of ulceration as well as new abnormal signal changes in revealed that the mucosal ulcer appeared deeper and was associ-

years after completion of radiotherapy, he developed acute onset smoking cessation which remained a challenge for him. Two residual carcinoma. Continued monitoring of the area showed per-

Figure 1. Sagittal view of radiotherapy planning computerized tomography (A) depicting the original gross tumor volume (colour wash) and 70 Gy isodose line encompassing the anterior components of C2–C3 vertebral bodies where osteomyelitis occurred. Sagittal (B) and axial (C) fat-saturated T2-weighted magnetic resonance images show evolving tumor ulceration along the posterior oropharyngeal wall (arrows).
recovery of cranial nerve findings and resolution of the EBV titres on all subsequent assays.

Five months after completion of concurrent CRT, the patient presented with rapidly progressive right-sided otitis externa, facial pain and restricted neck flexion with torticollis. Clinical examination showed an edematous auditory canal with no osseous exposure. Necrotic debris was evident throughout the nasopharynx without obvious signs of recurrence on flexible nasopharyngoscopy. Repeat EBV titres were performed to rule out recurrent disease and remained undetectable. MRI revealed diffuse swelling and enhancement involving bilateral petrous apices and the right masticator space with extension into the right external auditory canal that had received at least 66 Gy radiotherapy dose. Mild enhancement and edema was also seen in the left nasopharynx.

Fig. 2. Magnetic Resonance Image (MRI) demonstrates edema in the C2–C3 vertebrae with intact endplate margins (A). Loss of disc space height between C2 and C3 with endplate irregularity is evident and mild pressure on the subarachnoid space from an anterior epidural phlegmon has developed 3 months later (B). Enhancing epidural phlegmon (long arrow) is also evident in the anterior epidural space (C) and epidural phlegmon surrounding the vertebral arteries (short arrows) (D). The findings are typical of a discitis-osteomyelitis complex.

Fig. 3. Axial (A) and Coronal (B) MRI imaging shows nasopharyngeal carcinoma with extension into the right cavernous sinus, juxtaposed to the pituitary gland. The region of osteomyelitis was encompassed in the 66 Gy (inner thin line) radiotherapy volume (C).

Fig. 4. Follow up contrast enhanced axial T1 weighted (A and B) and fat-saturated axial T2 weighted image (C) shows diffuse enhancement of the right external auditory canal and right masticator space. There is tissue ulceration and necrosis in the right posterolateral nasopharynx (white arrow). The T2 image shows a preservation of the tissue planes in the right masticator space supporting an inflammatory process rather than tumor infiltration. An indium-111 white blood cell scan (D) shows uptake in the region of the right masticator space, nasopharynx and right central bony skull base. These findings also favor an infectious process.
with more than 3 years since completion of her antimicrobial treatment for her deep-seated skull base infection. No signs of disease are apparent and all cranial nerve deficits have resolved completely with complete return of ocular muscle function, eye opening, and return of function of the previously paralysed right tongue.

**Discussion**

Osteomyelitis, an infectious process of osseous structures (bone and marrow) is often associated with bony destruction [7]. It is a different bone entity from osteoradionecrosis (ischemic necrosis of the irradiated bone) albeit sharing somewhat similar signs and symptoms. While osteoradionecrosis is often chronic, osteomyelitis has a predilection to acute sequelae requiring urgent intervention. This clinical entity was initially described in the writings of Hippocrates in 5th century BC and later termed “osteomyelitis” by Parisian surgeon Auguste Nélaton in 1844 [8]. Vertebral osteomyelitis, also referred to as pyogenic spondylitis, often entails the involvement of two endplates of adjacent vertebra due to the vascular anatomy of this region. The pathogenesis of osteomyelitis and in particular, vertebral osteomyelitis, may be precipitated by haematogenous seeding from a distant infected area, direct inoculation from trauma or invasive procedures, or contiguous spread from an adjacent area of infection [9]. Radiation could also predispose patient to osteomyelitis due to radiation-induced stromal and vascular fibrosis resulting in increased risk of bacterial or candida colonization and infection on the adjacent mucosal membrane [10]. Treatment varies from non-invasive (e.g. antimicrobial therapy, hyperbaric oxygen therapy) to invasive surgical interventions.

The two cases included in this report are likely a consequence of ulceration in the adjacent mucosa that provides an entry portal for infection into the bone marrow and surrounding tissues juxtaposed to bone and/or intervertebral disc spaces. Thus, one might consider surgical closure as an option to prevent further progression to osteomyelitis. While local flap reconstruction can be considered in this situation, most experienced oncological and reconstructive surgeons recognize that local flap viability in a high dose radiation field is unreliable and may carry substantial risk of new wound healing problems. An additional issue is concern about potential persisting disease where early recurrence could be camouflaged by well-intended but putative approaches to repair residual post-radiotherapy ulceration that generally resolves with conservative management. Guidelines supporting a prophylactic surgical approach in this setting are unavailable. For this reason, close clinical surveillance was pursued in these two cases.

Osteomyelitis in the head and neck region is rare and mostly occurs in the mandible, and only rarely in the cervical spine or temporal bone [11]. Due to its proximity to intracranial critical structures, osteomyelitis in the skull base region could carry potentially lethal consequences. For example, in the area of skull base, vascular complications such as mycotic aneurysm, infectious arteritis or arterial rupture in association with bony infection represent a realistic risk, especially to the intra-petrous and parapharyngeal internal carotid artery. Paralysis (25% rate overall, highest in cervical vertebrae) and death (11%) have also been reported in cases of vertebral osteomyelitis [12]. Radiation-induced osteomyelitis near the skull base region (temporal bone and C2–C3 cervical vertebrae) presents unique challenges in diagnosis and treatment. Early detection and timely intervention is critical. For acute osteomyelitis, initiating a course of antimicrobial therapy urgently is paramount to avoid severe detrimental outcomes [12].

Diagnosis of osteomyelitis in some head and neck cancer patients is challenging due to limitations in anatomic accessibility to obtain a tissue diagnosis to rule out possible disease recurrence. Surgical intervention would also be undesirable in this region due to anatomical constraints. A relatively sudden onset of deep intense pain associated with suggestions of inflammation such as spasm and edema should trigger suspicion and investigation. Radiological assessment by an experienced oncologic head and neck neuroradiologist with MRI is the most sensitive and non-invasive method for the diagnosis of osteomyelitis [13]. Common imaging characteristics include decreased signal intensity in the vertebral bodies and disc, and loss of endplate definition on T1-weighted images; increased disc and/or osseous signal intensity on T2-weighted images; and contrast enhancement of the bone. These characteristics were seen in both cases in this report, enabling prompt and accurate diagnosis of a potentially life-threatening infection. In vitro labeled leukocyte imaging performed with indium-111 tagged leukocytes was utilised for the second patient and may further aid in diagnosis. This modality provides improved specificity in comparison to bone scan but does not visualize osseous detail or differentiate between soft tissue infections and osteomyelitis [14].

A tissue diagnosis or microbial aspiration for cultures is preferred to ensure accurate diagnosis and appropriate pathogen-directed antimicrobial therapy. However, the complicated anatomy of the head and neck often makes instrumentation in this area precarious. Microbial cultures were not obtained in either of the presented cases due to the potential risks associated with procedures of the upper cervical spine and base of skull, and the risk of infection. In such instances, empiric antimicrobial therapy directed at potential pathogens should be initiated by an infectious disease specialist [9]. Our cases were treated in this manner leading to good outcomes in both instances and with eradication of the infectious process at subsequent prolonged follow up. Additional approaches dealing with chronic radiation injury that might be considered include hyperbaric oxygen and vasoactive agents (e.g. pentoxifylline) combined with anti-oxidants (e.g. tocopherol) [15], but were neither employed nor necessary in these two cases. However, if utilized, such approaches should not undermine the need for urgent and appropriate antimicrobial therapy to address established osteomyelitis.

A high degree of vigilance is required to diagnose osteomyelitis in patients with malignant disease due to potential masking of clinical and radiological signs by treatment or cancer-related sequelae. In particular, care must be taken to distinguish this rare clinical entity from recurrent disease, as provision of anticancer therapies in the setting of osteomyelitis may intensify the infectious process and would be contraindicated. Patients who develop head and neck malignancies secondary to heavy smoking may also have significant peripheral vascular disease which may further contribute to a reduction in local tissue circulation leading to vascular insufficiency as was evident in Case 1. Moreover, the proximity of the irradiated bone and soft tissues to surrounding anatomical structures such as inflamed and infected pharyngeal, mastoid and paranasal sinuses, and nasal tissues provide potential portals of infection. In addition, continued tobacco use has been associated with increased incidence of grade 3–4 late toxicity, especially fibrosis following chemoradiation [16].

**Conclusions**

Osteomyelitis is a rare but potentially life-threatening condition in certain anatomic regions of head and neck which should be considered in the differential diagnosis of new or evolving post-radiotherapy osseous changes, particularly when changes are seen in regions juxtaposed to bone with potential portals for infection such as persistent mucosal ulceration following high dose (chemo-)radiotherapy. A high index of suspicion must be main-
tained for such cases and timely referral to a surgical oncologist and infectious diseases specialist, for prolonged intravenous antibiotics, is paramount in achieving satisfactory clinical outcomes. Further, optimization of baseline health status and promotion of smoking cessation should be initiated in all patients. Failure to identify and properly treat this entity would be expected to result in severe consequences.

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Conflict of interest

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