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Review

Cervical osteomyelitis: A new identity of dreaded complication following pharyngeal cancer treatment

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ABSTRACT

Background: Cervical osteomyelitis following the treatment of pharyngeal cancer with laryngectomy and chemoradiotherapy is poorly reported.
Methods: Six cases of cervical osteomyelitis occurring over a 1-year period are described herein. These are reviewed alongside four cases reported previously in the literature.
Results: Among the total 10 cases, the average age of the patients was 58.7 years. The period between laryngectomy and the diagnosis of cervical osteomyelitis was on average 3 years and 1 month and the male to female sex ratio was 9:1. Two patients had a history of cervical fistula with an esophageal prosthesis, one had a spontaneous cervical fistula, one had a pharyngeal cutaneous fistula, and one had an esophageal prosthesis without any fistula. At the time of diagnosis, seven had a history of cervical pain (70%) and nine had a neurological deficit (90%). Seven patients (70%) underwent surgery; one (10%) was contraindicated for a general anesthetic and two (20%) died before any intervention. The indication for surgery was a neurological deficit for six patients (60%) and the requirement for lavage and debridement for two patients (20%). The average length of antimicrobial treatment was 12.7 weeks. The outcome was favorable for six patients. Four patients died.
Conclusions: Cervical osteomyelitis is a serious but rarely reported complication following the treatment of pharyngeal cancer with chemoradiotherapy and laryngectomy. Cervical pain was the first sign to appear, sometimes 1 year before any other sign. Physicians should be aware of this dreaded complication, which is probably underdiagnosed and is related to an increased mortality rate.

Contents

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Introduction

Cervical osteomyelitis following the treatment of pharyngeal cancer with laryngectomy, radiotherapy, and chemotherapy is poorly reported (Skaf et al., 2010; Prasad et al., 2007; Kremers et al., 2015). The cases of six patients treated with laryngectomy and chemoradiotherapy for laryngeal or pharyngeal cancer, complicated by cervical osteomyelitis, are reported. These cases are reviewed alongside four cases reported previously in the literature (Biller et al., 1971; Buruma et al., 1979; Ell et al., 1992).

Materials and methods

The study center is the referral center for bone and joint infections in the south of France and is located in Marseille University Hospital. The study design was approved by the institutional review board. A retrospective review of the six cases of vertebral osteomyelitis with positive culture following pharyngeal cancer treatment with laryngectomy and chemoradiotherapy, managed between January 2015 and December 2017, was performed. A review of the four cases reported previously in the literature was also conducted.

The diagnosis of vertebral osteomyelitis was based on the patient's medical history, including clinical evidence of infection based on biological and radiological data, with $\geq$2 positive blood cultures or $\geq$2 positive cultures from deep samples from surgical or percutaneous biopsy, to exclude contaminating bacteria.

After incubation, the bacterial species were identified through conventional phenotypic identification or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonik). Complete 16S rRNA gene sequencing and real-time PCR assays targeting *Staphylococcus aureus* were performed on bacterial colonies for the unknown bacteria identified through MALDI-TOF MS and on deep samples that were negative on culture.

Each patient's medical history was evaluated, to assess factors such as demographic characteristics, comorbidities, and clinical characteristics. The antimicrobial and/or surgical treatment approaches used in each case and the outcome were also reviewed and recorded.

Results

Clinical characteristics

Among the total 10 cases, the average age of the patients was 58.7 years. The period between laryngectomy and diagnosis of cervical osteomyelitis was on average 3 years and 1 month and the male to female sex ratio was 9:1. Two patients had a history of cervical fistula with an esophageal prosthesis, one had a spontaneous cervical fistula, one had a pharyngeal cutaneous fistula, and one had an esophageal prosthesis without any fistula. At the time of diagnosis, seven had a history of cervical pain (70%) and nine had a neurological deficit (90%).

Microbiological characteristics

Surgical bone cultures were positive in 90% of cases. Blood cultures were positive for three out of seven patients (42.8%). Surprisingly, the pathogens detected did not belong to the oropharyngeal flora: *Streptococcus constellatus* (three patients), *Enterobacter cloacae* (one patient), *Escherichia coli* (one patient), *Pseudomonas aeruginosa* (two patients), *Enterococcus faecalis* (one patient), *Staphylococcus epidermidis* (one patient), mucormycosis (one patient), *Enterococcus faecium* (one patient), coagulase-negative Staphylococcus (one patient), *S. aureus* (one patient). The infection was monomicrobial in six patients, polymicrobial in three patients, and culture-negative in one.

Medical and surgical treatment

All patients underwent antimicrobial therapy, except for two patients who died before any treatment. The average length of treatment was 12.7 weeks (range 4–24 weeks). The antimicrobial therapies are show in Table 1. Seven patients (70%) underwent surgery; one (10%) was contraindicated for a general anesthetic and two (20%) died before any intervention. The indication for surgery was a neurological deficit for six patients (60%) and the requirement for lavage and bacteriological documentation because of the patient's worsening condition in two (20%). The six patients (60%) who underwent an operation had a posterior arthrodesis. Furthermore, five patients (50%) had a local bone biopsy (two patients, two times), one patient (10%) underwent two lavages, and another patient (10%) had a simple needle aspiration.

Clinical outcomes

The outcome was favorable for four patients, and one patient with a long period of follow-up showed no sign of recurrence. One patient died after 3 months of care, of an uncontrolled infection further complicated by Lemierre's syndrome. One patient suffered a hypertensive cerebral hemorrhage 1 month after being discharged. Another patient died of septic shock a few days after admission. Another died of hypoxemia arrest 1 month after discharge. The remaining patient died of complications of his neurological involvement.

Discussion

Cervical vertebral osteomyelitis is a rarely reported but serious complication following the treatment of pharyngeal carcinoma with laryngectomy and chemoradiotherapy. It appears that only four cases of this disease in adults have been reported previously. This article reports six new cases occurring over a 1-year period. In the context of laryngeal or pharyngeal cancer treatment with chemoradiotherapy and pharyngolaryngectomy, the presence of cervical pain, fever, and/or neurological signs should lead to early imaging to confirm the diagnosis. Cervical pain was the first sign to appear, sometimes 1 year before any other sign. In addition, an esophageal prosthesis could be a risk factor for cervical infection; osteomyelitis after this type of surgery has been reported previously (Mullen et al., 2013). Unlike some other investigator teams, we did not retain patients with cervical osteomyelitis after a second invasive procedure (Espitalier et al., 2016). Treatment in a neurological surgery center appears to be essential, in order to stabilize the spine while documenting the infection. In this context

Table 1
Demographic characteristics, clinical features, treatment, and outcomes of the 10 patients with cervical osteomyelitis following pharyngeal cancer treatment with laryngectomy and chemoradiotherapy.

Case	Age (years), sex	Comorbidities	Pharyngeal cancer			Cervical osteomyelitis						Outcome
			Localization	TNM[a]	Treatment	Time to diagnosis	Clinical signs	Localization	Pathogens	Surgical treatment	Duration of AT (weeks)	
1, PR	63, M	Smoking, alcohol	Tonsillar, PS, palate	Not known	LRG, RT, CHT	5 years	Fever, cervical pain	C3–C4	*S. constellatus* *S. epidermidis* *E. cloacae*	LD, PA, laminectomy, LD × 2	24	Died
2, PR	53, F	Smoking, alcohol	Hypopharynx	T4N0M0	LRG, RT, CHT	4 years	Fever, syncope, quadriparesis	C3–C5	None	LD, PA, laminectomy	8	Cured, fistula
3, PR	55, M	Smoking	Hypopharynx	Not known	LRG, RT, CHT	4 months	Cervical pain, fever, quadriplegia	C7–T2	*S. constellatus*	LD, PA, laminectomy	13.5	Cured, paresthesia
4, PR	65, M	Pulmonary tuberculosis, cirrhosis, smoking	Hypopharynx	T4N2c	LRG, RT, CHT, ER	2 years	Paresthesia, cervical pain	C5–T1	*P. aeruginosa* *E. faecalis*	LD, PA, laminectomy	6	Cured
5, PR	67, M	Smoking, alcohol, HBP	Hypopharynx	T4aN1M0	LRG, RT, CHT, EP	2 years	Fever	C5–C6	*S. epidermidis*	Contraindicated	Ongoing	Being treated, no relapse
6, PR	62, M	Smoking, alcohol	Hypopharynx	T4N0M0	RT, LRG	6 years	Swallow disorder, cervical pain, paresthesia	C6–C7	*E. faecium*	LD, PA, laminectomy	12	Died
Buruma et al. (1979)	60, M	Tuberculous lymphadenopathy	Hypopharynx	Not known	RT, LRG	11 years	Horner syndrome, quadriparesis, cervical pain, fever	C3–C4	Mucormycosis (post-mortem)	None	None	Died
Ell et al. (1992)	51, M	HBP, smoking	RVF	T2N0M0	RT, LRG	4 months	Fever, cervical pain, paresthesia (left arm)	C6–C7	CoNS *E. coli*	LD, PA, laminectomy, bone graft (iliac crest), 6 weeks of traction	Not known	Cured
Biller et al. (1971), case 1	59, M	Not known	Right lateral PS	Not known	RT, skin graft reconstruction and Negus stent	1 month	Swallow disorder, cervical pain, paresthesia	C6–C7	*S. aureus*	Needle aspiration, Crutchfield tongs (1 month), four-poster Bruce (1 year)	Not known	Cured
Biller et al. (1971), case 2	52, M	Not known	Palate, hypopharynx, right PS	Not known	RT, partial pharyngectomy	2 months	Fever, hemiparesis	C5–C7	*P. aeruginosa*	Refused by patient	None	Died

AT, antimicrobial therapy; CHT, chemotherapy; CoNS, coagulase-negative Staphylococcus; *E. cloacae*, *Enterobacter cloacae*; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*; EP, esophageal prosthesis; ER, esophageal reconstruction; F, female; HBP, high blood pressure; LD, lavage and debridement; LRG, laryngectomy; M, male; PA, posterior arthrodesis; *P. aeruginosa*, *Pseudomonas aeruginosa*; PLP, partial laryngopharyngectomy; PR, present report; PS, pyrifom sinus; RT, radiotherapy; RVF, Right vocal fold/cord; *S. aureus*, *Staphylococcus aureus*; *S. constellatus*, *Streptococcus constellatus*; *S. epidermidis*, *Staphylococcus epidermidis*.
[a] TNM, TNM classification.

of pharyngeal cancer with previous radiotherapy and surgery, we recommend posterior arthrodesis only.

Microbial documentation is necessary to guide antimicrobial therapy. We recommend blood culture, along with surgical or percutaneous biopsies (five samples) with aerobic, anaerobic, and fungal cultures. If cultures are negative, we recommend molecular biology with 16S rRNA gene sequencing and real-time PCR assays targeting *S. aureus*. Antimicrobial therapy should be adapted to polymicrobial infections and maintained over several weeks in order to obtain a definitive cure. We recommend initial antimicrobial therapy with piperacillin, tazobactam, and vancomycin for 2 weeks and then two oral antimicrobial agents, if possible, after identification. If identification is not possible, we recommend that antimicrobial therapy is focused on oral streptococci and negative bacilli, for example with co-trimoxazole and clindamycin. The duration of therapy should be 6 weeks in the absence of any surgical device or 3 months if an arthrodesis has been performed. All of these recommendations are consistent with those of the Infectious Diseases Society of America (Berbari et al., 2015).

Physicians should be aware of this dreaded complication, which is probably underdiagnosed (we diagnosed six cases over a period of 1 year) and is related to a high mortality (40%). It appears that early diagnosis and management improve the prognosis, but more extensive studies are required to confirm this finding.

In conclusion, in the context of laryngeal or pharyngeal cancer treatment with laryngectomy, the presence of cervical pain, fever, and/or neurological signs should lead to early imaging to confirm the diagnosis. Cervical pain was the first sign to appear in previous cases, sometimes presenting 1 year before any other sign. In addition, an esophageal prosthesis could be a risk factor for cervical infection. Treatment at a neurological surgery center appears to be essential, in order to stabilize the spine while documenting the infection. Precise microbial documentation is a crucial step in the management of these infections because the bacteria identified have not been those of the oropharyngeal flora. Antimicrobial therapy should be adapted to polymicrobial infections and maintained over several weeks in order to obtain a definitive cure. Physicians should be aware of this dreaded complication, which is probably underdiagnosed and is related to a high mortality (40%). It appears that early diagnosis and management improve the prognosis.

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Ethics

This study was approved by the institutional research ethics board and the patients signed a written informed consent form.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Emmanuel Zamparini (MD): clinical data collection; involved in drafting and revising the manuscript. Piseth Seng (MD, PhD): involved in drafting and revising the manuscript. Matthieu Bardou (MD): involved in clinical data verification, revising the manuscript. Nicolas Fakhry (MD, PhD): involved in clinical data verification, revising the manuscript. Thomas Graillon (MD): involved in clinical data verification, revising the manuscript. Stéphane Fuentes (MD, PhD): involved in clinical data verification, revising the manuscript. Patrick Dessi (MD, PhD): involved in clinical data verification, revising the manuscript. Andreas Stein (MD, PhD): approved the final version to be published. All authors read and approved the final manuscript for this submission.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.01.006.

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