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

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TITLE ‘ Cervical osteomyelitis: A new identity of dreaded complication following pharyngeal cancer treatment.’

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RUNNING HEAD: ‘Cervical osteomyelitis following pharyngeal cancer treatment with chemoradiotherapy and laryngectomy’

AUTHORS' CONTRIBUTIONS

- Dr Emmanuel Zamparini (MD): 1st author, clinical data collection; involved in drafting and revising the manuscript.

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- Dr Piseth Seng (MD, PhD): 2nd and corresponding author; involved in drafting and revising the manuscript.
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- Pr Andreas Stein (MD, PhD): last author approved the final version to be published

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ETHICS

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

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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KEYWORDS: Cervical osteomyelitis; Laryngectomy; Larynx carcinoma; cervical cancer; Infection

ABSTRACT

Background. Cervical osteomyelitis following pharyngeal cancer treatment with chemoradiotherapy and laryngectomy is poorly reported.

Methods. We herein report the cases of six cases over a one-year period and we also reviewed the four cases reported in literature.

Results. Among the ten cases, the average age was 58.7 years, the period between laryngectomy and diagnosis of cervical osteomyelitis was 3 years and 1 month and the sex ratio was 9 men /1 woman. 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 deficiency (90%). Seven patients (70%) underwent surgery; one (10%) was contraindicated for a general anesthetic, two (20%) died before any intervention. The indications for surgery were: a neurological deficit for six patients (60%) and two (20%) needed a lavage and debridement. Average length of antimicrobial treatment was of 12.7 weeks. The outcome was favorable for 6 patients. Four patients died.

Conclusions. Cervical osteomyelitis is a serious but rarely reported complication following pharyngeal cancer treatment with chemoradiotherapy and laryngectomy. Cervical pain was the first sign to appear, sometimes one year before any other sign. Physicians should be aware of this dreaded complication witch is probably underdiagnosed and witch is related to an increased mortality rate.

1 Introduction

Cervical osteomyelitis following pharyngeal cancer treatment with laryngectomy, radiotherapy and chemotherapy is poorly reported (1,2,3). We herein report the cases of six patients treated by laryngectomy for laryngeal or pharyngeal cancer, with chemoradiotherapy complicated by cervical osteomyelitis and review 4 more cases of literature (4,5,6).

2 Materials and methods

Our center is the referral center for bone and joint infections in south of France located in the Marseille university hospital. This study design was approved by the review board of our institute. We retrospectively reviewed the 6 cases of vertebral osteomyelitis with positive culture following pharyngeal cancer treatment with chemoradiotherapy and laryngectomy managed between January 2015 and December 2017. We also reviewed the 4 cases of literature.

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

After incubation, the bacteria species was identified through conventional phenotypic identification or MALDI-TOF MS (Brüker Daltonik). A complete 16S rRNA gene sequencing and real-time PCR assays targeting *Staphylococcus aureus* performed on bacteria colony for the unknown bacteria identified through MALDI-TOF MS and on deep samples which were negative at culture.

We evaluated each patient's medical history, assessing factors such as demographic characteristics, comorbidities, and clinical. We reviewed the antimicrobial and/or surgical treatment approaches used in each case and the outcome.

3 Results

3.1. Clinical characteristics

Among the ten cases, the average age was 58.7 years, the period between laryngectomy and diagnosis of cervical osteomyelitis was 3 years and 1 month and the sex ratio was 9 men /1 woman. 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 deficiency (90%).

3.2. Microbiological characteristics

Surgical bone cultures were positive in 90 % of cases. Blood cultures were positive for three out of seven patients (42.8%). Surprisingly, pathogens detected did not belong to the oropharyngeal flora: *Streptococcus constellatus* (3 patients), *Enterobacter cloacae* (1 patient), *Escherichia coli* (1 patient), *Pseudomonas aeruginosa* (2 patients), *Enterococcus faecalis* (1 patient), *S. epidermidis* (1 patient), Mucormycosis (1 patient), *Enterococcus faecium* (1 patient), coagulase negative staphylococci (1 patient), *Staphylococcus aureus* (1 patient). Infection was monomicrobial for six patients, polymicrobial for three patients, and culture negative for one**.**

3.3 Medical and surgical treatment

All patients underwent antimicrobial therapy excepted two who died before any treatment. Average length of treatment was of 12.7 weeks [4 weeks – 24 weeks]. Antimicrobial therapy are show in table 1. Seven patients (70%) underwent surgery; one (10%) was contraindicated for a general anesthetic, two (20%) died before any intervention. The indications for surgery were: a neurological deficit for six patients (60%) and two (20%) needed a lavage and bacteriological documentation because the patient's condition were worsening. The six patients (60%) who underwent an operation had a posterior arthrodesis, 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.

3.4 Clinical outcome

The outcome was favorable for 4 patients, and one patient who had a follow-up for a long period didn't show any sign of recurrence. One died after 3 months of care, of an uncontrolled infection further complicated by Lemierre's syndrome. One patient presented a hypertensive cerebral hemorrhage, one month after being discharged. One died of septic shock few days after admittance. Another died of hypoxemia arrest one month after discharge. One died of complication of his neurological involvement.

4 Discussion

Cervical vertebral osteomyelitis is rarely reported but a serious complication following the treatment of pharynx carcinoma treated with chemoradiotherapy and laryngectomy. To the best of our knowledge, only four cases of this disease have been previously reported in adults. In this paper, we report six new cases over a one year period. In the context of laryngeal or pharyngeal cancer treatment with chemoradiotherapy and pharyngo-laryngectomy, cervical pain, fever or neurological signs should lead to early imaging to confirm the diagnosis.

Cervical pain was the first sign to appear, sometimes one year before any other sign. In addition, esophageal prosthesis could be a risk factor of cervical infection; osteomyelitis after this kind of surgery has been previously reported (7). Unlike some other team's, we did not retain patients with cervical osteomyelitis after a second invasive procedure (8). Treatment in a neurological surgery center seems compulsory, in order to stabilize the spine while documenting the infection. In this context of pharyngeal cancer with previous radiotherapy and surgery, we recommend posterior arthrodesis only. Microbial documentation is necessary to guide antimicrobial therapy. We recommend to do blood culture, surgical or percutaneous biopsies (five samples) with aerobic, anaerobic and fungal cultures. If cultures are negatives, we recommended molecular biology with 16S rRNA gene sequencing and real-time PCR assays targeting *Staphylococcus aureus*. Antimicrobial therapy should be adapted to polymicrobial infections and maintained over several weeks in order to obtain a definitive cure. We recommended initial antimicrobial therapy with piperacillin, tazobactam and vancomycin for two weeks and after identification, two oral antimicrobial therapy if it's possible. If identification it's not possible, we recommended antimicrobial therapy focus on oral streptococci and negative bacilli such as Cotrimoxazol and clindamycin. The duration of therapy should be 6 weeks without any surgical device or 3 months if arthrodesis had been performed. All of these recommendations are consistent with those of Infectious Diseases Society America (9). Physicians should be aware of this dreaded complication witch is probably underdiagnosed (we diagnosed six cases over a year in our center) and witch is related to a high mortality (40%). It seems that early diagnosis and management improve the fatal issue, but more extensive studies are requested to confirm this finding.

5 Conclusion

In the context of laryngeal or pharyngeal cancer treatment with laryngectomy, cervical pain, fever or neurological signs should lead to early imaging to confirm the diagnosis. Cervical pain was the first sign to appear, sometimes one year before any other sign. In addition, esophageal prosthesis could be a risk factor of cervical infection. Treatment in a neurological surgery center seems compulsory, in order to stabilize the spine while documenting the infection. Precise microbial documentation is a crucial step in the management of those infections because bacteria found are not those from 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 witch is probably underdiagnosed and witch is related to a high mortality (40%). It seems that early diagnosis and management improve the fatal issue.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

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ETHICS

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

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

Cases number	Ages (years), Sex	Comorbidities	Localization	TNM Classification	Treatment of cancer	Time to diagnosis	Clinical signs	Localization	Pathogens	Surgical Treatment	AT duration (weeks)	Outcomes
Our 1st case	63, M	Smoking, alcohol	Tonsillar PS, Palate	n. k.	LRG, RTH, CTH	5 years	Fever, cervical pain	C3-C4	*S. constellatus* *S. epidermidis* *E. cloacae*	LD, PA, laminectomy LD x 2	24	Deceased
Our 2nd case	53, F	Smoking, alcohol	Hypopharynx	T4N0M0	LRG, RTH, CTH	4 years	Fever, syncope, quadriparesis	C3-C5	None	LD, PA, laminectomy	8	Cured, fistula
Our 3rd case	55, M	Smoking	Hypopharynx	N. K.	LRG, RTH, CTH	4 months	Cervical pain, fever, quadriplegia	C7-T2	*S. constellatus*	LD, PA, laminectomy	13.5	Cured, paresthesia
Our 4th case	65, M	Pulmonary tuberculosis, cirrhosis, Smoking	Hypopharynx	T4N2c	LRG, RTH, CTH, ER	2 years	Paresthesia, cervical pain	C5-T1	*P. aeruginosa* *E. faecalis*	LD, PA, laminectomy	6	Cured
Our 5th case	67, M	Smoking, alcohol, HBP	Hypopharynx	T4aN1M0	LRG, RTH, CTH, EP	2 years	Fever	C5-C6	*S. epidermidis*	CI	On going	Being treated, no relapse
Our 6th case	62, M	Smoking, alcohol	Hypopharynx	T4N0M0	RTH, LRG	6 years	Swallow disorder, cervical pain, paresthesia	C6-C7	*E. faecium*	LD, PA, laminectomy	12	Deceased
Buruma et al. (1979)	60, M	Tuberculous lymphadenopathy	Hypopharynx	n. k.	RTH, LRG	11 years	Horner syndrome, quadriparesis, cervical pain, fever	C3-C4	*Mucormycose* (post-mortem)	None	None	Deceased
Ell et al. (1992)	51, M	HBP, Smoking	RVF	T2N0M0	RTH, LRG	4 months	Fever, cervical pain, paresthesia (left arm)	C6-C7	CNS *E. coli*	LD, PA, laminectomy, bone graft (iliac crest), 6 weeks of traction	n. k.	Cured
Biller et al. (1971) case-1	59, M	n. k.	Right lateral PS	n. k.	RTH, Skin graft reconstruction and Negus stent	1 month	Swallow disorder, cervical pain, paresthesia	C6-C7	*S. aureus*	Needle aspiration, Cruchfield tongs (1 M), Four-poster bruce (1 Y)	n. k.	Cured
Biller et al. (1971) case-2	52, M	n. k.	Palate Hypopharynx Right PS	n. k.	RTH Partial pharyngectomia	2 months	Fever, hemiparesis	C5-C7	*P. aeruginosa*	Refused by patient	None	Deceased

n. k.: not known, RTH: Radiotherapy, CTH: Chemotherapy, LRG: laryngectomy, EP: Esophageal prosthesis, ER: Esophageal reconstruction, HBP: high blood pressure, PLP: partial laryngopharyngectomy, CNS: Coagulase negative staphylococci, LD: lavage and debridement, PA: posterior arthrodesis, CI: contraindicated, AT: antimicrobial therapy