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par

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TITRE

Actinomycose de l'oreille moyenne : étude rétrospective multicentrique observationnelle en région Grand Ouest entre 2007 et 2017 (ActiGO) et revue de littérature.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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A mes amis, fidèles au poste, comme un phare dans la nuit.

Summary:

I/ Abstracts :

Résumé

Objectif : Les bactéries du genre *Actinomyces* sont exceptionnellement responsables d'infections de l'oreille moyenne. Le diagnostic clinique et bactériologique est complexe et le traitement repose sur une antibiothérapie prolongée. L'objectif de ce travail était de décrire une série de cas d'actinomycose de l'oreille moyenne comparée à la littérature.

Matériels et méthodes : Nous avons réalisé une étude rétrospective des cas d'actinomycose de l'oreille moyenne diagnostiqués entre 2007 et 2017 dans la région Grand Ouest. Les variables analysées comprenaient des données cliniques (symptômes, localisation), microbiologiques (espèce, technique d'identification) et thérapeutiques (chirurgie, durée et modalités d'antibiothérapie, évolution). Ces données ont été confrontées à une revue de littérature.

Résultats : Nous avons recueilli 12 cas régionaux et 42 issus de la littérature. L'âge médian des patients était de 24,5 ans. 35 étaient de sexe masculin. Une otorrhée chronique avec hypoacousie étaient retrouvée chez 27 patients et un cholestéatome chez 14 patients. 19 patients avaient une atteinte non compliquée de l'oreille moyenne et 35 présentaient une complication neurologique et/ou ostéoarticulaire. Une mastoïdectomie a été réalisée chez 46 patients. La durée médiane d'antibiothérapie était de 90 jours avec une évolution favorable sur le plan microbiologique chez 34 patients.

Conclusion : Les infections à *Actinomyces* de l'oreille moyenne touchent principalement les hommes jeunes. Les formes compliquées sont fréquentes. L'évolution semble favorable y compris à l'issue de traitements antibiotiques de courte durée, possiblement du fait de l'implication d'espèces potentiellement moins virulentes, plus fréquemment identifiées.

Mots clés : *Actinomyces*, oreille moyenne, mastoïdite, cholestéatome.

Substantial abstract:

Introduction : Les bactéries du genre *Actinomyces* sont des germes anaérobies de la flore commensale de l'oropharynx, du tube digestif et du tractus génital. Habituellement faiblement pathogènes, elles peuvent engendrer des infections chroniques à l'occasion d'une rupture de la barrière muqueuse. Parmi les atteintes de la sphère ORL, l'actinomycose de l'oreille moyenne est exceptionnelle et l'absence de signes évocateurs peut s'accompagner d'un retard diagnostique et de complications loco-régionales (osseuses et/ou intracrâniennes). Par ailleurs, compte tenu d'une croissance anaérobie préférentielle lente, au sein de prélèvements fréquemment plurimicrobiens, le diagnostic microbiologique est souvent complexe. Le traitement repose sur une antibiothérapie prolongée souvent associée à un drainage chirurgical. L'objectif de ce travail était de décrire une série de cas d'infections de l'oreille moyenne à *Actinomyces* dans la région Grand Ouest, et de confronter ces données à une revue de littérature.

Matériel et Méthodes : Nous avons réalisé une étude rétrospective multicentrique (Angers, Nantes, Orléans, Rennes et Tours) des cas d'actinomycose de l'oreille moyenne diagnostiqués entre 2007 et 2017. Les patients ont été identifiés à partir des prélèvements microbiologiques. Les variables analysées comprenaient des données cliniques (comorbidités, symptômes, localisation), microbiologiques (espèce, technique d'identification, co-infection) et thérapeutiques (chirurgie, durée et modalités d'antibiothérapie, évolution). Ces données ont été confrontées à une revue de littérature.

Résultats : Nous avons recueilli 12 cas en région Grand Ouest sur la période considérée et 42 issus de la littérature. L'âge médian des patients était de 24,5 ans [11-40]. 35 (65%) étaient de sexe masculin. Une otorrhée chronique avec hypoacousie étaient retrouvées chez 27 patients (50%) et un cholestéatome chez 14 patients (26%). 23 patients ont rapporté de la fièvre ou une fébricule (43%). 19 patients (35%) présentaient une atteinte non compliquée de l'oreille

moyenne et 35 (65%) une complication neurologique (n=23) et/ou ostéoarticulaire (n=29). Parmi les 23 *Actinomyces* identifiés, *A. turicensis* (n=7), *A. meyeri* (n=4), *A. europaeus* (n=4) et *A. israelii* (n=3) étaient les plus couramment retrouvés. Les espèces détectées étaient différentes entre les patients issus de la revue de littérature et ceux de notre cohorte française. Les prélèvements étaient polymicrobiens dans 19 cas (35%) avec principalement des micro-organismes commensaux de la flore oro-pharyngée. Le diagnostic était exclusivement histologique chez 28 patients (52%). Une culture positive était retrouvée chez 25 patients (46%). Une mastoïdectomie a été réalisée chez 46 patients (85%). Plus de la moitié des patients (56%) a nécessité au moins deux interventions chirurgicales. 39 patients ont reçu des antibiotiques (72%) avec de la pénicilline en première intention dans 30 cas. La durée médiane d'antibiothérapie était de 90 jours [42-180] avec une évolution favorable sur le plan microbiologique chez 34 patients (63%) et sans aucune séquelle dans 22 cas (41%). Concernant les séquelles, une hypoacousie (n=8), une paralysie faciale (n=2) ou oculomotrice (n=2), une otorrhée (n=1) ou des troubles cognitifs (n=1) ont été rapportés. Une rechute ou récurrence est survenue dans 5 cas, soit en l'absence de chirurgie ou en raison d'un geste incomplet, soit à cause d'une antibiothérapie trop courte (durée médiane du traitement initiale : 21 jours). Parmi les 8 cas de décès, 7 sont survenus avant 1945 et l'utilisation en routine de la pénicilline. La durée médiane de suivi était de 12 mois [6-18].

Conclusion : Les infections à *Actinomyces* de l'oreille moyenne sont rares et touchent principalement les hommes jeunes dans un contexte de cholestéatome dans un quart des cas. Les formes compliquées sont fréquentes. Depuis l'avènement des antibiotiques, l'évolution semble favorable y compris à l'issue de traitements de courte durée. Ceci pourrait en partie être expliqué par l'essor de la spectrométrie de masse facilitant l'identification d'espèces plus variées potentiellement moins virulentes.

Actinomycosis of the middle ear: A retrospective, multicentre, observational study in a French region between 2007 and 2017 (ActiGO) and a review of the literature.

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Abstract:

Introduction: Actinomyces is a genus of commensal anaerobes gram-positive bacteria, sometimes responsible for cervicofacial, thoracic or abdominal chronic infections. Middle ear localization is rare. Clinical and microbiological characteristics are complex and treatment usually implies a long-term antibiotic therapy. The aim of this work was to describe a French cohort of middle ear actinomycosis confronted to a literature-based cohort.

Material and Methods: This retrospective descriptive study included actinomycotic middle ear infections diagnosed between 2007 and 2017 in the "Grand Ouest" French region. Clinical (symptoms, localization), microbiological (species, identification techniques), treatment (surgery, antibiotic stewardship) and outcome data were systematically recorded. These data were confronted to a literature-based cohort.

Results: 54 cases were collected: 12 from our cohort and 12 from literature. The median age was 24.5 years. 35 were men. Chronic otorrhea with hearing loss was found for 27 patients and cholesteatoma for 14 patients. 19 patients presented an uncomplicated middle ear infection whereas 35 had neurological and/or bone involvement. 46 patients underwent mastoidectomy. The median antibiotic therapy duration was 90 days with microbiological success for 34 patients.

Conclusion: Middle ear actinomycosis classically concerns young men. Complicated forms are common. Outcome seems quite good with medico-surgical approach. Some patients received a short-term antibiotic therapy with good results, probably due to less-pathogenic species.

Key words: *Actinomyces*, middle ear, mastoiditis, cholesteatoma

II/ Manuscript:

1. Introduction:

Actinomycosis is a rare, chronic granulomatous disease described for the first time in man by Israel in 1878 (1,2). *Actinomyces* is a genus of filamentous, Gram-positive, non-acid-fast anaerobic or facultative anaerobic bacteria from the Actinobacteria class. Commensal microorganism of the oropharynx, the gastrointestinal and urogenital tracts, they are generally of low pathogenicity (3,4). However, in the setting of tissue injury and mucosal barrier disruption, they can be responsible for torpid infections (5,6). Humans are a natural reservoir and no person-to-person transmission has been documented (7,8). The cervicofacial region is the most common site involved (50-60%), thorax and abdomen being less frequent (5,8–10). Predisposing conditions for cervicofacial infection include poor oral hygiene (dental caries, gingivitis, chronic tonsillitis), oral mucosa trauma (gingival trauma, dental extraction, surgery, neoplastic disease, or irradiation), male sex, *diabetes mellitus*, alcoholism, immunosuppression and malnutrition (7,10–12). More than 40 species of *Actinomyces* are known, and *Actinomyces israelii* and *gerencseriae* are the two main human pathogens, found in 70% of the infections of the cervicofacial area (5,8,9,13). Actinomycotic infections are frequently polymicrobial: *Aggregatibacter actinomycetemcomitans*, *Prevotella*, *Streptococcus*, Enterobacteriaceae, *Peptostreptococcus* or *Staphylococcus* are usually associated (9,11,14). The co-isolates involved depend on the organ infected and promote the infection by inhibiting host defenses, reducing local oxygen tension and favouring biofilm formation (5,14,15).

Clinical signs include painless infiltration and induration which form multiple abscesses and draining sinus tracts (5). In almost 50% of the orofacial cases, the maxilla and lower mandible are involved (14). Actinomycotic infection ignores tissue planes and can extend into local

structures such as muscles and bones. Lymphadenopathy are unusual until delayed stages (5,9) and hematogenous spread is rare (16). Malignancy, tuberculosis or *Nocardia* related infections are the most frequent differential diagnosis (5,16). Imaging techniques can be useful to guide a biopsy or reveal the extension of the infection (9).

Diagnosis is complex because of unspecific symptoms, atypical course and fastidious bacterial growth. Actually, *Actinomyces* cultures are negative in 50-70% of cases, due to previous antibiotic therapy, inadequate culture conditions, short-term incubation or inhibition by concomitant microorganisms (8,14,17). Therefore, the histopathological examination is usually informative, classically revealing a yellowish "sulfur granule" formation (mycelial fragments surrounded by peripheral clubs) or gram-positive filamentous organisms (5,7,9). Modern identification methods (mass spectrometry, polymerase chain reaction, 16S rRNA gene sequencing) now permit a faster, more accurate diagnosis and new *Actinomyces* species are described and involved in clinical infections (5,16,18–20).

Effective treatment usually consists in prolonged penicillin therapy (from 6 months to one year or more (16,21–24)). Shorter courses of treatment (two to six weeks) have been reported in cases where local extension was limited and/or extended surgery was used (25–27). Combination with a beta-lactamase inhibitor to treat penicillin-resistant aerobic or anaerobic companion bacteria is contested (21,28). Surgery is often indicated for curettage of bone, resection of necrotic tissue, excision of sinus tracts and drainage of abscesses (5,7,9,26,29) but there is no consensus. Some consider surgical debridement is required because of *Actinomyces* capacity to survive in poor vascularized tissues, where antibiotics are not effective (30). Others think surgery is only necessary when a tissue sample is needed for diagnosis or in case of antibiotic failure (14,31,32). Nowadays, antibiotic therapy and surgical indication are individualized, considering the infection (site and severity) and response to treatment (5,9). Prolonged follow-up is recommended to monitor for recurrences (9).

Prognosis is excellent when actinomycosis is diagnosed and appropriately treated whereas mortality was high in the pre-antibiotic era.

Actinomycosis of the middle ear and mastoid is a rare entity. Less than 50 cases have been reported in the literature. The signs of the otological form have been described by Beck in 1906 (33). The routes for contamination of the middle ear are unknown. Three are mentioned: extension from the pharynx via the Eustachian tube, directly through the external auditory canal, or via hematogenous dissemination (34,35). The clinical presentation is an indolent, chronic, suppurative otitis refractory to standard antibiotic treatment. The misreading of this diagnosis is often associated with delayed or complicated infections (osteitis or intracranial abscesses), potentially responsible for morbid consequences (36–38).

We report here cases of actinomycosis of the middle ear from a French cohort confronted to literature data in order to improve understanding of this infrequent disease. The objectives of this study were 1) to describe epidemiological, clinical and microbiological characteristics of middle ear actinomycosis and their complications, and 2) to report the proposed treatment (antibiotic treatment, surgery) and the associated outcome.

2. Material and methods:

Middle ear actinomycosis cases of 5 French hospitals (Angers, Nantes, Orleans, Rennes, and Tours) were compiled in a retrospective, observational, non-interventional multicentre study conducted from January 2007 to December 2017. All patients having cervicofacial and central nervous system (CNS) samples positive in culture for *Actinomyces* in each microbiology laboratory were reviewed. Inclusion criteria were: 1) exclusive middle ear location or cerebral and/or osteo-articular infection with a middle ear origin, 2) documented by at least one *Actinomyces* positive microbiological sample, 3) in child or adult patients. Patients' data were retrospectively extracted from their electronic medical file in each hospital by their corresponding physician. Epidemiological characteristics (age, sex), clinical presentation (diagnostic delay, prior antimicrobial therapy or ear surgery, immunodeficiency, dental health, presence of cholesteatoma, fever, otorrhea, hearing loss, otalgia, mastoid swelling, headache, nystagmus, vertigo, complications (osteitis, vein thrombosis, facial paralysis, intracranial abscess, subdural empyema or meningitidis), other actinomycotic location), microbiological results (species, diagnostic and identification methods, companion bacteria) and therapeutic management (surgery, antibiotic stewardship, outcome) were collected. The local ethics committee approved the study (approval n° 2017 058) and a declaration to the French data protection agency was done (CNIL, approval n° 2017_104). Each patient received information and non-opposition forms.

In parallel, a systematic literature review of middle ear actinomycosis was achieved. Cases were identified by searching electronic database (Medline) and screening references and google scholar citations of the selected articles. Studies meeting the following criteria were included: *Actinomyces* middle ear infection, concerning children or adults, published in case reports, in English or French language. Complicated intracranial or osseous actinomycosis cases were only accepted if there was a middle ear involvement. Animal cases were excluded.

Abstracts, posters and literature reviews without case reports were not included. We used the following algorithm: ("actinomyces" OR "actinomycosis" OR "actinomycetale" OR "streptothrix" OR "streptomyces" OR "actinomycotic") AND ("middle ear" OR "otitis media" OR "otitis" OR "mastoiditis" OR "temporal bone" OR "brain" OR "brain abscess" OR "meningitis" OR "subdural empyema"). Last search was run on 2017, September 5Th. One reviewer assessed the eligibility of each article in a standardized manner. Titles and abstracts were screened then relevant full-text examined. Information concerning articles (title, author, journal, study design, year of publication) and patients' data (above epidemiological, clinical, microbiological and therapeutic variables, identical to the retrospective study) were extracted in a data sheet.

Continuous variables were expressed as median and interquartile range and categorical variables as numbers and proportions. Comparisons between categorical variables were performed with Fisher's exact test. A p value < 0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using R program (3.0).

3. Results:

3.1 Methodology:

In our 5 regional hospitals, in cooperation with microbiology laboratories, 58 cervicofacial samples with positive *Actinomyces* culture were detected (Nantes (n=28), Tours (n=10), Orléans (n=8), Angers (n=7) and Rennes (n=5)). Finally, 12 patients presented the inclusion criteria: 6 from Tours, 5 from Nantes and 1 from Rennes. None were identified in Angers or Orléans. The flow chart of the patients evaluated for inclusion is presented in Figure 1. The main characteristics (sex, age, presence of otorrhea, hearing loss, fever, cholesteatoma, *Actinomyces* location, specie, identification technique, antibiotics (type and duration), surgery, outcome) of each case are reported in Table 1. Medical treatment data were missing or incomplete for 3 patients and surgical care for 2 patients. Outcome was unknown for 2 patients.

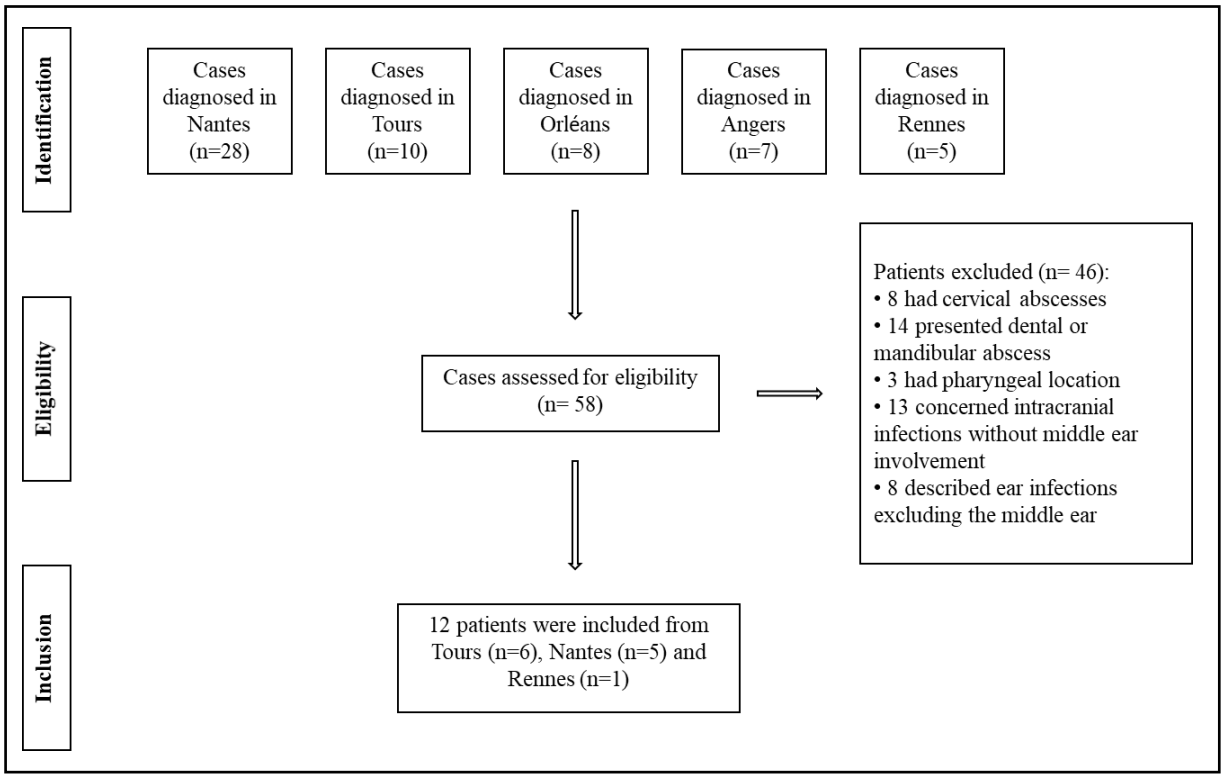

Figure 1. Flow chart of the cohort patients screened for inclusion

Table 1. Overview of the 12 middle ear infection cases from our regional cohort.

y*: year of publication, y: year, CNS: Central Nervous System, &: and, /: then, d: days.

Town	Sex	Age (y)	Location	Otorrhea	Hearing loss	Fever	Cholesteatoma	Documentation	Species	Antibiotherapy	Duration (d)	Mastoidectomy	Outcome
Tours	F	16	mastoid	Y	Y	Y	Y	culture	*europaeus*	amoxicillin-clavulanate	14	Y	hearing loss
Tours	M	26	mastoid	Y	Y	N	Y	culture	*turicensis*	amoxicillin	180	Y	hearing loss/otorrhea
Tours	F	17	mastoid, osteitis, CNS	Y	NA	Y	Y	culture	*europaeus & turicensis*	amoxicillin-clavulanate	NA	Y	hearing loss
Tours	M	35	mastoid	Y	Y	N	N	culture	*turicensis*	amoxicillin-clavulanate	90	Y	hearing loss
Tours	M	27	mastoid, CNS	Y	Y	N	Y	culture	*europaeus*	bactrim	270	Y	memory loss
Tours	M	17	mastoid, osteitis	Y	NA	Y	Y	culture	*meyeri*	cefotaxime	7	Y	recurrence
Rennes	F	7	mastoid	Y	Y	Y	N	culture	*sp*	amoxicillin-clavulanate	14	Y	good
Nantes	M	38	mastoid	Y	Y	NA	Y	culture	*turicensis*	amoxicillin-clavulanate	18	Y	NA
Nantes	F	21	mastoid, osteitis, CNS	Y	Y	Y	N	culture	*meyeri*	meropenem	NA	NA	NA
Nantes	F	79	mastoid, CNS	NA	Y	NA	Y	culture	*europaeus*	amoxicillin & dalacin	180	NA	good
Nantes	M	36	mastoid	Y	Y	NA	Y	culture	*turicensis*	NA	NA	Y	good
Nantes	M	25	mastoid, osteitis, CNS	Y	Y	NA	Y	culture	*turicensis*	NA	120	Y	hearing loss

Using the Medline algorithm aforementioned, 478 articles were found. 26 were included. Of the 452 excluded articles, 278 were irrelevant, 147 concerned intracranial actinomycosis without middle ear involvement, 15 described cervicofacial infections apart from middle ear, 11 were pertinent but excluded because of foreign language or unavailability and 1 was duplicated. Google scholar citations of the 26 articles selected were explored and 9 more articles were added. Subsequently, studying the reference lists of these 35 articles, 4 other articles were identified. Finally, we included 39 manuscripts, corresponding to 42 cases (Figure 2). All studies reported retrospective clinical cases. Three of them contained 2 cases (35,39,40) and 8 combined a literature review. 10 articles were published before 1945 and routine penicillin use. The main characteristics of each case appear in Table 2. Table 3 compares patients' characteristics from the literature review and our regional cohort.

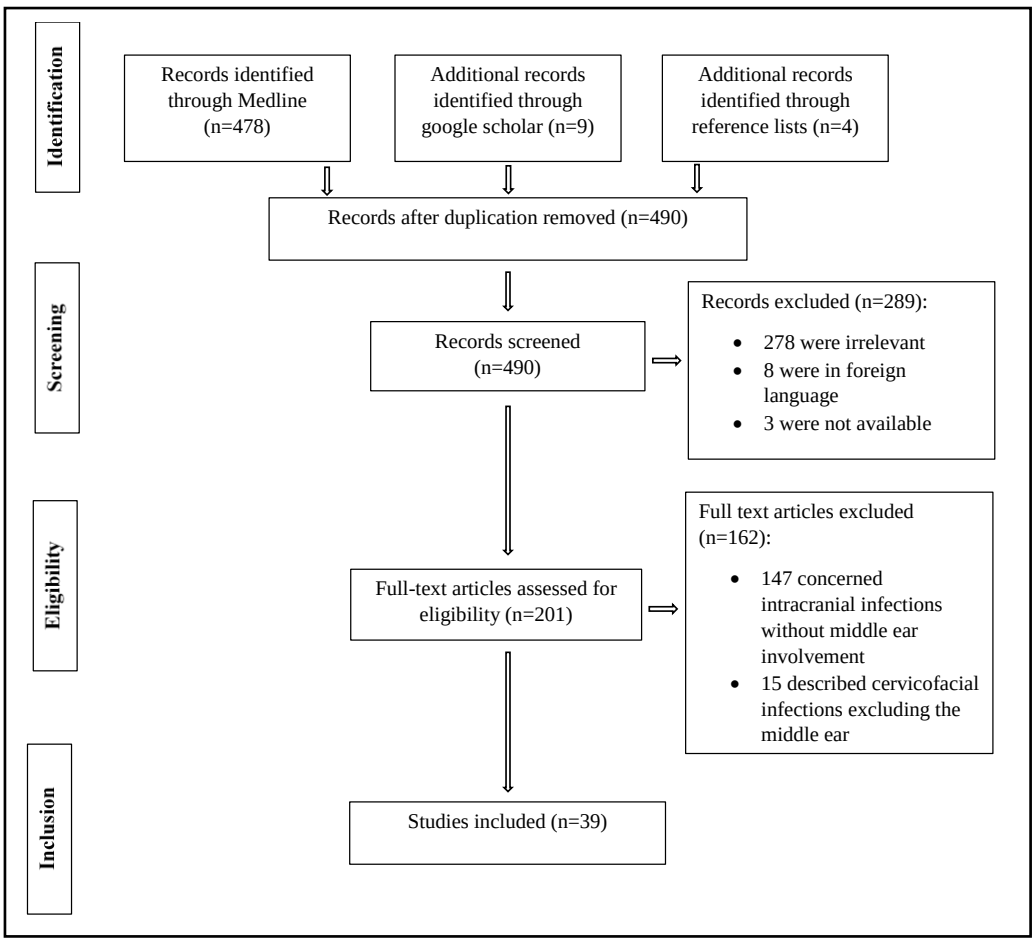

Figure 2. Flow chart of the study selection.

Table 2. Overview of the 42 middle ear infection cases from literature review.

y*: year of publication, y: year, CNS: Central Nervous System, &: and, /: then, d: days.

Author, y*	Sex	Age (y)	Location	Otorrhea	Hearing loss	Fever	Cholesteatoma	Diagnosis	Species	Antibiotherapy	Duration (d)	Mastoidectomy	Outcome
Ajal, 1997	M	10	mastoid, osteitis	Y	Y	NA	NA	histology	NA	penicillin	90	Y	good
Beck, 1906	M	54	mastoid, osteitis	NA	Y	NA	NA	histology	NA	N	NA	Y	death
Boor, 1998	M	9	mastoid, osteitis	NA	NA	NA	NA	histology	NA	penicillin	NA	Y	good
Brown, 1942	M	21	mastoid, osteitis, CNS	NA	NA	Y	NA	histology	NA	N	NA	Y	death
	M	45	mastoid, osteitis, CNS	NA	NA	Y	NA	histology	NA	N	NA	Y	death
Budenz, 2010	F	12	mastoid, osteitis, CNS	NA	Y	Y	NA	histology	NA	clindamycin	222	Y	good
Cann, 1931	F	9	mastoid, CNS	NA	NA	Y	NA	histology & culture	NA	N	NA	N	death
Chakroun, 1995	M	38	mastoid, osteitis	Y	NA	Y	NA	histology	NA	cotrimoxazole	365	Y	good
Dornan, 1979	F	27	mastoid	NA	Y	NA	NA	histology & culture	*israelii*	tetracycline	42	N	good
Drury, 1929	F	35	mastoid, osteitis, CNS	N	Y	Y	NA	culture	NA	N	NA	Y	death
Fletcher, 1956	M	73	mastoid, osteitis	Y	NA	Y	NA	histology	NA	penicillin/aureomycin/chloramphenicol/sulfisoxazole	NA	Y	death
Gazzano, 2010	NA	8	mastoid	Y	Y	NA	Y	histology	NA	amoxicillin	21	Y	recurrence
Haiman, 1939	M	10	mastoid, osteitis	Y	NA	Y	NA	culture	NA	N	NA	Y	good
Heineman, 1962	M	14	mastoid, osteitis, CNS	NA	Y	Y	NA	culture	NA	penicillin/sulfisoxazole/tetracycline	21	Y	hearing loss
	F	53	mastoid, osteitis, CNS	NA	NA	Y	NA	culture	NA	penicillin & doxycycline	14	Y	good
Hoshino, 1996	F	24	mastoid	Y	Y	NA	NA	histology & culture	*gerencseriae*	cefuroxime axetil	NA	N	recurrence
Jamjoom, 1994	M	19	mastoid, CNS	NA	NA	N	NA	culture	*israelii*	penicillin	30	Y	good
Kakuta, 2013	M	55	mastoid	Y	Y	NA	NA	histology	*meyeri*	amoxicillin	42	Y	hearing loss
Kullar, 2013	F	9	mastoid	Y	Y	NA	Y	histology	NA	amoxicillin	180	Y	good
Lee, 2015	F	60	mastoid	Y	Y	NA	NA	histology	NA	cefcapene	180	Y	good
Leek, 1974	F	11	mastoid	Y	Y	NA	NA	histology	NA	penicillin	90	Y	good
	M	20	mastoid	Y	Y	NA	NA	histology	NA	penicillin	120	Y	recurrence
Lezcano, 2014	M	10	mastoid, osteitis	NA	Y	Y	NA	histology	NA	amoxicillin-clavulanate	180	Y	hearing loss
Martin, 1931	M	22	mastoid, osteitis, CNS	N	NA	Y	NA	histology	NA	N	NA	Y	death
Mehta, 2007	M	11	mastoid, osteitis	Y	Y	NA	NA	histology	NA	ampicillin-sulbactam	63	Y	facial nerve palsy
Miglets, 1983	M	37	mastoid, osteitis	Y	Y	NA	NA	histology & culture	*propionicus*	penicillin	90	Y	good
Miller, 2014	M	5	mastoid, osteitis, CNS	Y	NA	Y	Y	culture	*turicensis*	amoxicillin	230	Y	gaze palsy
Odom,1944	M	38	mastoid	Y	Y	NA	NA	culture	*albus*	N	NA	N	recurrence
Olson, 1989	M	8	mastoid	Y	Y	Y	NA	histology	NA	penicillin	180	Y	NA
O'Malley, 1924	M	67	mastoid, osteitis	NA	NA	Y	NA	histology	NA	NA	NA	N	NA
Ono, 2006	M	31	mastoid	Y	Y	N	NA	histology	NA	amoxicillin	64	NA	good
Oudidi, 2005	F	58	mastoid	NA	Y	NA	Y	histology	NA	amoxicillin	120	Y	good
Oukessou, 2015	M	30	mastoid, osteitis	Y	Y	NA	NA	histology	NA	amoxicillin	165	Y	facial nerve palsy
Pulcini, 2011	M	43	mastoid, osteitis	Y	Y	NA	NA	culture	*meyeri*	clindamycin & rifampicin	150	Y	good
Risch, 1939	M	42	mastoid, osteitis	NA	NA	Y	NA	culture	*farcinicus*	N	NA	Y	good
Salipante, 2014	M	46	mastoid, osteitis	NA	NA	Y	NA	gram & NGS	*israelii*	amoxicillin-clavulanate	NA	Y	NA
Shelton, 1988	M	10	mastoid	Y	Y	NA	Y	histology	NA	penicillin	180	Y	good
Shishegar, 2009	M	24	mastoid	NA	Y	NA	NA	histology	NA	NA	NA	Y	NA
Sivarajasingam, 2007	M	78	mastoid, osteitis	Y	NA	NA	NA	histology	NA	ampicillin	42	Y	NA
Subha, 2004	F	19	mastoid	Y	Y	NA	NA	histology	NA	penicillin	42	Y	good
Tarabichi, 1993	F	7	mastoid, osteitis	Y	Y	NA	NA	histology	NA	NA	120	Y	good
Townrow, 1945	M	64	mastoid, osteitis, CNS	Y	NA	Y	NA	histology	NA	N	NA	Y	death

Table 3. Comparison between literature review and cohort

M: man, F: female, y: year, n: number of patients, CNS: Central Nervous System, d: day

	Total (N=54)	**Literature (N=42)**	**Case serie (N=12)**	p
Sex Ratio M/F	2.1	2.4	1.4	
Median age (IQR)	24.5 (11-41)	24 (10-44)	25.5 (17-35)	> 0.1
Location n (%)				
Osteitis	29 (54%)	25 (60%)	4 (33%)	> 0.1
CNS	16 (30%)	11 (26%)	5 (41%)	> 0.1
Otorrhea n (%)	35 (65%)	24 (57%)	11 (92%)	0.06
Hearing loss n (%)	36 (67%)	26 (62%)	10 (83%)	> 0.1
Fever n (%)	23 (43%)	18 (43%)	5 (42%)	> 0.1
Cholesteatoma n (%)	**14 (26%)**	**5 (12%)**	**9 (75%)**	**< 0.01**
Documentation n (%)	**25 (46%)**	**13 (31%)**	**12 (100%)**	**< 0.01**
Species (n)				
turicensis	7	1	6	
meyeri	4	2	2	
europaeus	4	0	4	
israelii	3	3	0	
Treatment n (%)				
Antibiotic	39 (72%)	29 (69%)	10 (83%)	> 0.1
Penicillin	30 (56%)	23 (58%)	7 (58%)	> 0.1
Median duration (d)	90	105	90	> 0.1
Mastoidectomy	46 (85%)	36 (86%)	10 (83%)	> 0.1
Outcome n (%)				
Microbiological cure	34 (63%)	25 (60%)	9 (75%)	> 0.1
Sequelae	**12 (22%)**	**6 (14%)**	**6 (50%)**	**0.03**
Recurrence	5 (9%)	4 (10%)	1 (8%)	> 0.1
Death	8 (15%)	8 (19%)	0	> 0.1
Missing data	7 (13%)	5 (12%)	2 (17%)	> 0.1

3.2 Epidemiological and clinical data:

The total study population consisted of 35 men and 19 women, corresponding to a male/female sex ratio of 2.1. The median age of patients was 24.5 years [interquartile range: 11-40]. All patients presented a middle ear infection, which was bilateral in 3 cases. In 29 cases (54%), temporal bone, petrous bone and/or basal skull osteitis were associated. 16 patients (30%) had a CNS involvement: cerebral abscess (n=11), meningitis (n=4) or both (n=1). Osseous and CNS invasion were combined in 11 cases. A cervical or intracranial vein thrombosis was described in 8 patients. Extension work-up revealed other actinomycotic localization (lung, nasopharynx, parotid gland, tonsil, external otitis, artery and bloodstream) for 7 patients (13%).

Regarding potential risk factors, bad oral status was reported for 10 patients (19%) and previous ear surgery was noted for 18 (33%). 6 patients (11%) were immunocompromised: 3 were diabetic and 3 received corticosteroids for more than a month. 14 had homolateral cholesteatoma (26%). Association with cholesteatoma was significantly more common in our regional cohort than in the literature review: 9 cases out of 12 (75%) versus 4 cases out of 42 (12%), $p<0.05$. Furthermore, 19 patients were treated with antibiotics (oral or drops) prior to diagnosis (35%). *Actinomyces* culture was nevertheless successful in 12 of these cases (63%). Concerning the period between symptoms onset and diagnosis, the median delay was 9 months [2.75-24], using data from 27 patients. A chronic otitis or otorrhea history without further detail was noted for 20 patients. Data were unknown in 7 cases. The median delay was 20 months [3-96] for patients with uncomplicated middle ear infection (with 9 chronic otitis), 10 months [2.5-24] for patients with osteitis without CNS location (with 6 chronic otitis) and 5 months [2.75-10] for patients with CNS infection (with 8 chronic otitis).

As regards to clinical signs, 36 patients complained about hearing loss (67%), 35 patients about otorrhea (65%), 23 about otalgia (43%), 19 about headache (35%), 5 about vertigo (9%)

and 23 presented fever or low-grade fever (43%). Otorrhea and hearing loss were more frequent in the case series than in literature review (respectively 92% and 83% versus 57% and 62%) but clinical signs were also more detailed.

Mastoid and/or cervicofacial abscesses were noticed in 17 cases (31%). 23 patients (43%) described neurological symptoms. Among patients with CNS involvement (n=16) were reported: somnolence or coma (n=9), hemiplegia or hemiparesis (n=5), gaze palsy or diplopia (n=4), homonymous hemianopsia (n=2), anisocoria (n=2), aphasia or dysarthria (n=2), dizziness (n=2), nystagmus (n=2), ataxia (n=1), cerebellar syndrome (n=1) and seizure (n=1). Among patients with peripheral nervous system damage, we noted facial nerve palsy (n=6), cranial nerve palsy from skull base osteitis (n=2), gaze palsy (n=2) and vertigo (n=1). Post-operative facial and gaze palsy were excluded. Among the 23 patients with fever or low-grade fever, 19 had a CNS location and/or mastoid abscess (83%).

3.3 Microbiology:

23 *Actinomyces* were identified in 22 patients (one sample was positive for *A. turicensis* and *A. europaeus*). The most common species found were *A turicensis* (n=7), *A. meyeri* (n=4), *A. europaeus* (n=4) and *A. israelii* (n=3). We found no association between localization (mastoid, osteitis or CNS) and *Actinomyces* species (Table 4). When comparing the literature review and our French cases, the *Actinomyces* species detected were different. In the review, identification was performed in 10 patients (24%) and the main species were *A. israelii* (n=3) and *A. meyeri* (n=2). In our regional cohort, 100% of *Actinomyces* were identified (n=13) and *A. turicensis* and *A. europaeus* represented 77% of the diagnosed species (respectively n=6 and n=4). Samples were polymicrobial in 19 cases (35%). The co-pathogens were mainly orofacial commensal microorganisms and the most common were *Fusobacterium* (n=5), *Streptococcus* (n=5), Enterobacteriaceae (n=5), *Staphylococcus* (n=2) and diverse anaerobes.

Diagnosis was strictly histological for 28 patients (52%). 25 (46%) had a positive culture, including all our regional cases. One diagnosis was suspected by gram stain and confirmed by next generation sequencing. Identification was performed by mass spectrometry (n=11) phenotypic methods (n=6), 16S rRNA gene sequence analysis (n=1) and next generation sequencing (n=1).

Table 4. *Actinomyces* distribution according to location.

CNS: Central Nervous System

location / specie	mastoid	osteitis	CNS	
			with osteitis	no osteitis
A. turicensis	n=4		n=3	
A.meyeri	n=1	n=1	n=1	
A. europaeus	n=1		n=2	n=1
A. israelii	n=1	n=1		n=1
A. albus	n=1			
A. farcinicus		n=1		
A. gerencseriae	n=1			
A. propionocus		n=1		
A. sp	n=1			

3.4 Treatment and outcome:

39 patients received antibiotics (72%). Among the 15 remaining patients: 10 were treated before 1945 and penicillin use and data were unknown for 5 patients. The median antibiotic therapy duration was 90 days [42-180], based on 35 patients' data. Penicillin or amoxicillin (whether or not associated with beta-lactamase inhibitor) were used as first-line antibiotics in 30 patients (56%). Alternative molecules consisted of cyclin (n=4), other B-lactams (n=4), clindamycin (n=3), cotrimoxazole (n=2), chloramphenicol (n=2), sulfisoxazole (n=2) and rifampicin (n=1); alone or in association. Within patients with simple mastoiditis, the median duration treatment was 90 days [31.5-180]. For patients with osteitis without CNS location, the median duration treatment was 105 days [63-165]. Among patients with CNS complication, the median antibiotic therapy was 150 days [25.5-226].

46 patients (85%) underwent mastoidectomy. One rejected adequate surgery after tympanotomy and myringotomy. If necessary, concurrent complications' surgery was done (abscess drainage, facial nerve decompression, External Ventricular Derivation…). 30 patients (56%) needed at least two surgeries.

22 patients fully recovered (41%), 12 suffered from sequelae (22%), 5 presented a recurrence (9%), 8 patients died (15%), and data were missing for 7 patients (13%). Before antibiotic therapy, mortality was significantly higher (70% versus 2%, $p < 0.005$). Indeed, all deaths were attributed to the actinomycotic infection and 7 of the 8 dead patients (87.5%) did not receive antibiotics. The last one had an extended osteitis with skull base involvement and died despite surgery and consecutive use of penicillin, aureomycin, chloramphenicol and sulfisoxazole (38) . Only one of the dead patients had no surgery. Sequelae described were hearing loss (n=8), facial nerve palsy (n=2), gaze palsy (n=1), chronic otorrhea (n=1) and memory loss (n=1). Among these patients, 10 had chronic otitis or otorrhea history. The 2 patients with residual facial nerve palsy had initially a temporal bone osteitis. Among patients with persistent hearing loss, 50% originally presented an uncomplicated middle ear infection. After-effects were more commonly found among patients from our cohort. This should be put into perspective with the cholesteatoma proportion.

Relatively few patients experienced microbiological failure. In cases of recurrences, the median initial diagnosis delay was 64.5 months [6-121.5]. Oral condition, immunosuppression or *Actinomyces* species (*A. meyeri* n=1, *A. albus* n=1, *A. gerencseriae* n=1), did not seem to be associated with recurrence. Two had cholesteatoma (40%). None of these patients suffered from intracranial complication, one presented osteitis (fifth case) and 4 had uncomplicated mastoid infections. The median first-line antibiotic duration was 21 days [7-120]. Two patients initially did not had surgery. Among them, one also initially refused antibiotic treatment. The first one was an 8-year-old girl. She received a 3-weeks amoxicillin

course after a mastoidectomy. Thereafter, she relapsed twice: first she took amoxicillin during 60 days, then amoxicillin and pristinamycin during 150 days (41). The second patient initially refused recommended surgery and antibiotics. After her recurrence, she accepted long-term oral cephalosporin (42). The third patient originally underwent tympanotomy with tube insertion and received penicillin for 120 days. After relapse, evolution went well (except hearing loss) through mastoidectomy and another penicillin course during 150 days (35). The fourth patient did not receive antibiotic treatment since he became ill in 1934. 3 months after diagnosis and phytotherapy, microbiological samples were still positive (43). The fifth patient had cholesteatoma complicated by mastoid abscess and temporal osteitis. He was treated by mastoidectomy and 7-day cefotaxime course. After additional amoxicillin therapy during 90 days, he still complained about recurrent otorrhea.

The median follow-up duration was 12 months [6-18].

4. Discussion:

Actinomycosis is a chronic infection, rarely involving middle ear. From our results, this specific location may typically concern young men with chronic otorrhea and hearing loss, associated with cholesteatoma in a quarter of patients. Complications seem common as more than half of the patients presented bone involvement and one third had a CNS location. Diagnosis is delayed by *Actinomyces* slow growth and the need for specific techniques to isolate the pathogen. Modern identification techniques tend to improve it. Antibiotic duration is varied, depending on medical teams and initial gravity but since antibiotics are used, prognosis is relatively good.

The current study describes 54 cases from a literature review (n=42) and from a French regional cohort (n=12). This is the most significant middle ear actinomycosis case series published to date. Combined with a literature review, it provides interesting data about this under-diagnosed infection.

Our work has several limitations. Firstly, this is an observational retrospective non-comparative study. Statistical analysis is limited by missing data and a restricted number of patients, which are not strictly comparable considering the location of the infection, *Actinomyces* species, diagnosis methods or treatment. However, we used restrictive definition criteria to compare the patients. Secondly, the literature review was made by only one reviewer and some studies remained unavailable.

Three middle ear actinomycosis risk factors seem to stand out: homolateral cholesteatoma, previous ear surgery and bad oral condition. Cholesteatoma is described in approximately a quarter of patients. Consequently, theories can be raised. On the one hand, it could exist a preferential association between cholesteatoma and *Actinomyces* (by creating a growing environment?). Actinomycotic infection and cholesteatoma could also be initially confounded

because of similar clinical presentation. On the other hand, actinomycosis is possibly responsible for cholesteatoma post-operative infection. Mehta et al (17) reported a temporal bone actinomycosis arisen 4 months after ventilation tube insertion and suggested a potential implication of surgery. Zitsch and Ozaki also submitted this idea in two articles about head and neck surgeries (44,45). A mucosal barrier disruption actually occurs during surgery and would favour *Actinomyces* infection. This refers to the second risk factor identified which is a previous ear surgery. The third one was poor dental health, in line with the assumption that *Actinomyces* extends to the middle ear from the pharynx via Eustachian tube as suspected in the case reported by Ono et al (30).

Modern identification techniques appear to be more effective than previously and extend the different *Actinomyces* species identified. According to Ng et al (20), Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is a promising tool for the identification of aero-tolerant *Actinomyces* species while Vitek MS database still need optimization for Lynch et al (46). Hall et al reported that amplified 16S rDNA restriction analysis is highly discriminatory for identification of *Actinomyces* species (47). Using this method, they noticed a predominance of *A. turicensis* (48) whereas *A. israelii* was previously considered as the most frequent specie involved in cervico-facial actinomycosis (13). *Actinomyces* species diagnosed in the literature study (mainly from anatomopathological laboratories) and in our cohort (strictly from microbiological laboratories) are different and potentially not comparable. Indeed, in a retrospective study, Clarridge et al (4) described that only *Actinomyces israelii* and *A. meyeri* were associated with sulfur granules in histological specimens. Moreover, Sabbe et al (49) assume that new described Actinomyces species or ALO (*Actinomyces*-like organisms) are less pathogen but of clinical relevance, since they sometimes are the only pathogen identified. Because of the *Actinomyces* genus classification complexity and misidentification risk, these results should be carefully considered.

B-lactams and especially penicillin are the first-line antibiotic therapy due to their effectiveness and tolerance. In case of allergy, tetracycline and tetracycline analogues, clindamycin, or macrolide antibiotics are suitable alternatives (50–52). Some publications described *Actinomyces* susceptibility *in vitro* to linezolid and tigecycline whereas fluoroquinolones have poor activity (18,22). These results should be treated with caution because there are no species-specific breakpoints for these antibiotic families. Moreover, a Moroccan paper reported four actinomycotic cerebral abscesses treated with fluoroquinolones during 8 to 14 weeks with a good outcome (53). The authors also suggested that antibiotic therapy could be shortened in immunocompetent patients in association with adequate surgery. This viewpoint is shared by Jamjoom et al who treated three *Actinomyces israelii* brain abscesses during 3 or 4 weeks and Ravindra who recently reported seventeen actinomycotic cerebral abscesses with a mean antibiotic duration of 8.4 weeks (27,54). Surgical stewardship is as well discussed in many articles. Some authors suggested that surgery is not mandatory in limited actinomycotic infections (52). Dailey and al presented an actinomycotic cerebral abscess cured with a minimally invasive surgical treatment combined with a long antibiotic course (6 months) (32). In opposite, Ravindra et al recently described 17 Actinomycotic cerebral abscesses; all patients underwent surgery (54). Besides treatment, surgery is useful for microbiological diagnosis especially in case of atypical microorganism such as *Actinomyces*. In that respect, Gruber et al described necrotizing otitis externa of fungal origin cured thanks to microbiological identification, permitted by surgical samples (55). Regarding specific medical history of patients presenting a primary treatment failure in our study, either antibiotic therapy duration seemed too short or surgery was partial or refused. Accordingly, both surgical and medical treatment seem complementary. Therapeutic decision is complex and based on actinomycotic location, physicians and surgeons' experience and clinical, microbiological and imaging response.

When actinomycosis is suspected, notably in cases of recurrent middle ear infections in young adults or difficult-to-treat cholesteatoma, an active cooperation between physicians, surgeons, microbiologists and pathologists could improve the diagnosis frequency. In order to facilitate *Actinomyces* detection, we recommend a minimally invasive surgery after antibiotic interruption and the use of metronidazole disk in anaerobic agar because of its natural resistance, combined with prolonged culture (at least 2 weeks). Concerning treatment, our opinion is that antibiotic therapy duration could be reduced to 6 weeks for uncomplicated middle ear actinomycosis and 3 months seem sufficient in case of CNS involvement or osteitis in association with the least invasive surgery possible, and an active imaging and clinical monitoring. This approach would need to be supported by a prospective surveillance of incident cases.

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36 pages – 4 tableaux – 2 figures

Résumé :

Objectif : Les bactéries du genre *Actinomyces* sont exceptionnellement responsables d'infections de l'oreille moyenne. Le diagnostic clinique et bactériologique est complexe et le traitement repose sur une antibiothérapie prolongée. L'objectif de ce travail était de décrire une série de cas d'actinomycose de l'oreille moyenne comparée à la littérature.

Matériels et méthodes : Nous avons réalisé une étude rétrospective des cas d'actinomycose de l'oreille moyenne diagnostiqués entre 2007 et 2017 dans la région Grand Ouest. Les variables analysées comprenaient des données cliniques (symptômes, localisation), microbiologiques (espèce, technique d'identification) et thérapeutiques (chirurgie, durée et modalités d'antibiothérapie, évolution). Ces données ont été confrontées à une revue de littérature.

Résultats : Nous avons recueilli 12 cas régionaux et 42 issus de la littérature. L'âge médian des patients était de 24,5 ans. 35 étaient de sexe masculin. Une otorrhée chronique avec hypoacousie étaient retrouvée chez 27 patients et un cholestéatome chez 14 patients. 19 patients avaient une atteinte non compliquée de l'oreille moyenne et 35 présentaient une complication neurologique et/ou ostéoarticulaire. Une mastoïdectomie a été réalisée chez 46 patients. La durée médiane d'antibiothérapie était de 90 jours avec une évolution favorable sur le plan microbiologique chez 34 patients.

Conclusion : Les infections à *Actinomyces* de l'oreille moyenne touchent principalement les hommes jeunes. Les formes compliquées sont fréquentes. L'évolution semble favorable y compris à l'issue de traitements antibiotiques de courte durée, possiblement du fait de l'implication d'espèces potentiellement moins virulentes, plus fréquemment identifiées.

Mots clés : *Actinomyces*, oreille moyenne, mastoïdite, cholestéatome

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