

CASE REPORT

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Meningitis due to *Gemella sp.* in a patient with severe ENT conditions: case report and review of the literature

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Abstract

In June 2022, a 73-year-old man with a history of laryngeal and esophageal carcinoma was admitted to the emergency unit with sudden fever, confusion, and general condition deterioration. Initial assessments showed a fever of 38.5 °C, elevated C-reactive protein (CRP) at 209 mg/L, and a neutrophil count of 10.4 G/L, with negative results for urine analysis, blood cultures, and multiple infectious pathogens, including *Legionella pneumophila*, pneumococcal antigen, and SARS-CoV-2. Computed tomography (CT) scans revealed no significant infectious focus.

Empirical treatment with Ceftriaxone and Ciprofloxacin was initiated. Despite treatment, the patient's condition remained unchanged, and a lumbar puncture revealed turbid cerebrospinal fluid (CSF) with 14,300 white blood cells (WBC)/mm³, predominantly neutrophils, elevated proteins, and decreased glucose. Gram staining suggested *Neisseria meningitidis*, but further testing was necessary. Antibiotic therapy was switched to Cefotaxime and Dexamethasone, and the patient was transferred to the Tropical and Infectious Disease Unit.

Multiplex PCR assays and additional CSF tests were negative for common pathogens. Sequencing of 16S ribosomal RNA identified *Gemella sp.* The patient's condition improved with continued Cefotaxime treatment, and he recovered without neurological sequelae. Subsequent dental CT revealed poor dental hygiene but no signs of osteo-meningeal breach or bone lysis.

A literature review identified 22 reported cases of central nervous system (CNS) infections caused by various *Gemella* species from 1980 to 2022. Of these, 59% presented with meningitis, and 41% had additional encephalitis or brain abscesses. Complete recovery occurred in 77% of cases, with 9% resulting in neurological damage and another 9% in fatal outcomes. Relapses occurred in 14% of the cases. The review highlighted that CNS infections by *Gemella spp.* primarily affect immunocompromised adults with ENT (ear nose throat) or neurological breaches, although some cases involved healthy individuals.

This case underscores the diagnostic challenges posed by uncommon pathogens like *Gemella* and highlights the utility of molecular microbiology in identifying causative agents, thus guiding appropriate treatment. The

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patient's history of ENT and esophageal cancers, along with recent radiotherapy and chemotherapy, likely contributed to the infection's development. The case emphasizes the importance of thorough investigation in febrile confusion cases and the potential role of *Gemella* spp. in CNS infections.

Keywords *Gemella* spp., *Gemella hemolysans*, Meningitis, Molecular biology, Microbiology, ENT conditions, Bacterial meningitis

Background

Meningitis is a life-threatening condition consisting in an inflammation of the meninges which can be suspected in attendance of meningism, and confirmed by cerebrospinal fluid (CSF) analysis [1]. The absence of central neurological signs help distinguish it from meningoencephalitis [2]. However, the high frequency of associated confusion in both cases, especially in elderly and patients with comorbidities, can lead to a prejudicial delay in diagnosis [3]. Meningitis is a condition with a reserved prognosis, without suitable treatment, and with a mortality rate of more than 20% and 30% sequelae for bacterial meningitis of all etiologies combined [1]. Bacterial meningitis is most often due to transient or permanent bacterial carriage in the ear, nose and throat (ENT) sphere with hematogenous dissemination or by contiguity from an ENT entry point. In France, the two bacteria most frequently involved are *Streptococcus pneumoniae* and *Neisseria meningitidis* [4] but many bacteria have the ability to pass the blood-brain barrier if conditions are favorable for their development, such as *Gemella* sp. in our case.

The genus *Gemella* is a rather recent taxon (1960) including 7 species: *G. haemolysans*, *G. morbillorum*, *G. bergeri*, *G. sanguinis*, *G. asaccharolytica*, *G. palaticanis*, *G. cuniculi*. (the last 2 being only found in animals). It was first described as *Neisseria hemolysans* in 1938 [5].

These bacteria are usually found in human oral cavities and upper respiratory tract as well as dental plaque, they are also commonly found in other mammals [6].

They are facultative anaerobic and Gram positive, although they can present as Gram variable (as shown in our case). They have been described as opportunistic pathogens that can cause infections in immuno-compromised patients or with favoring conditions such as valvular cardiopathy, ENT tumors and invasive procedures [7]. They can also cause superficial or deep abscess, meningitis and endocarditis [8]. They usually share the antibiotic sensitivity of oral *Streptococci* being sensitive to β -lactams, rifampicin, glycopeptides and resistant to aminoglycosides (low-level) and quinolones [9].

Case

In June 2022, a 73-year-old man was admitted to the emergency care unit presenting with sudden fever, confusion, and a deterioration of his general condition. His medical history included laryngeal squamous

cell carcinoma treated with partial laryngectomy and radio-chemotherapy in 2012, and esophageal carcinoma metastasized to the lungs, treated with radiotherapy, 5 Fluoro-uracil and Oxaliplatin.

Upon admission, the patient had a fever with a body temperature of 38.5 °C but was hemodynamically stable. Neurological examination revealed confusion without focal neurological signs. Laboratory tests showed an inflammatory syndrome with elevated C-reactive protein (CRP) at 209 mg/L and a neutrophil count of 10.4 G/L, with a slight procalcitonin (PCT) increase at 0.64 ng/mL. Urine analysis and cyto-bacteriological examination of the urine were negative. *Legionella pneumophila* and pneumococcal antigenuria (BinaxNOW, Abbott) as well as Covid-19 (SARS-CoV-2) and influenza PCR were negative. Standard and mycological blood cultures were also later found negative.

A thoracic, abdominal, and pelvic CT scan revealed a vesical globe and fecal stasis but no significant infectious focus. Given the febrile confusion without a clear infection site, empirical treatment with Ceftriaxone and Ciprofloxacin (considering potential prostatitis) was initiated before CSF was drawn.

Despite the initial treatment, the patient's condition remained unchanged the next day. Cerebral scan without prior injection was normal, notably without focal lesion or sign of brain herniation contraindicating lumbar puncture (LP).

Despite initial treatment, the patient's condition remained unchanged the next day. A non-contrast cerebral CT scan showed no focal lesion or sign of brain herniation, allowing for a lumbar puncture (LP). The CSF was turbid with 14,300 white blood cells (WBC)/mm³, predominantly neutrophils (around 90%). Biochemical analysis revealed CSF proteins of 3.52 g/L and decreased CSF glucose of 0.3 g/L. Gram staining showed many Gram-negative cocci in diplococcus form, suggesting an infection caused by *N. meningitidis*, although discolored *S. pneumoniae* could not be ruled out.

The diagnosis of meningitis led to a change in antibiotic therapy to Cefotaxime 360 mg/kg/day at meningeal doses (for a patient weighing 50 kg), along with a dose of Dexamethasone 10 mg intravenous (IV). The patient was later transferred to the Tropical and Infectious Disease Unit for continued IV antibiotic therapy while awaiting bacterial identification.

Table 1 Cases of central nervous system infections caused by <i>Gemella</i> species (reported as of Novembre 2022). API: analytical profile index, 16S rRNA: 16S ribosomal RNA.								
Article	Species	Means of identification	Morbidity factors	Potential favoring factors	Clinical presentation	Symptoms	Treatment (duration)	Outcome
Gomez Arroyo B, et al. 2021 [11]	<i>Gemella hemolysans</i>	Maldi-TOF	Clivus	Brain surgery	Meningitis	Headache	Vancomycin	Recovery
			Chordoma	Radiotherapy		Fever Vomiting	Meropenem Ampicillin Amikacin Meropenem Linezolid	
Riviere P, et al. 2020 [12]	<i>Gemella bergeri</i>	Maldi-TOF 16S rRNA sequencing	Type 2 Diabetes Hypertension	Ear cholesteatoma	Meningitis	Headache Dizziness Fever Vomiting	Cefotaxime Amoxicillin	Complete recovery with no long-lasting effects
Dominguez-Gil M, et al. 2018 [13]	<i>Gemella hemolysans</i>	Maldi-TOF	Hypophyseal adenoma	Transsphenoidal surgery	Meningitis	Fever Stiff neck	Vancomycin Ceftazidime Switched to Ceftriaxone	Complete recovery
Galen BT, et al. 2014 [14]	<i>Gemella hemolysans</i>	16S rRNA sequencing	Hypertension chronic obstructive pulmonary disease, pre-diabetes Abducens nerve palsy	Mucosal thickening of the maxillary sinuses	Meningitis	Decreased responsiveness Nausea Vomiting, Diarrhea Fever	Vancomycin Ceftriaxone Ampicillin	Complete recovery with no long-lasting effects
Hayashi T, et al. 2013 [15]	<i>Gemella hemolysans</i>	Not disclosed		Diffuse periodontitis Clivus osteomyelitis	Meningitis	Fever Headache	Ciprofloxacin (28 days) Ceftriaxone (28 days) then Doxycycline (35 days)	Relapse after 73 days, then recovery
Benedetti P, et al. 2009 [16]	<i>Gemella morbillorum</i>	API Gallery 16S rRNA sequencing	Tuberculosis	None disclosed	Acute meningitis, Cerebellar and brain abscess after relapse	Fever Headache Neck stiffness then Fever Dizziness Ataxia	Meropenem (3 weeks) Piperacillin/tazobactam (1 week) Penicillin Cefotaxime	Relapse after 2 months, Death
Villegas E, et al. 2008 [17]	<i>Gemella morbillorum</i>	Not disclosed	None disclosed	None disclosed	Meningitis hypophyseal haemorrhage	Headache Vomiting Fever Confusion Neck stiffness a bitemporal haemianopsia	Cefotaxime Vancomycin (6 days) Benzylpenicillin Gentamycin (2 weeks)	Recovery with chronic panhypopituitarism
Anil M, et al. 2007 [10]	<i>Gemella hemolysans</i>	API Gallery	Congenital heart disease	None disclosed	Meningitis	Fever Vomiting Loss of appetite	Ampicillin Cefotaxime (3 days) Linezolid Chloramphenicol (10 days)	Complete recovery with no long-lasting effects
Lopes, Armando, et al. 2007 [18]	<i>Gemella morbillorum</i>	Not disclosed	Congenital cardiac malformation	Dental procedure	Cerebral abscess	Headache Vomiting Fever Ataxia	Ceftriaxone Vancomycin Metronidazole (6 weeks)	Recovery

Table 1 (continued)

Article	Species	Means of identification	Morbidity factors	Potential favoring factors	Clinical presentation	Symptoms	Treatment (duration)	Outcome
Liberto, Maria Carla, et al. 2006 [19]	<i>Gemella morbillorum</i>	API Gallery	None disclosed	None disclosed	Cerebral abscess	Fever Headache Nausea Lethargy	Meropenem Metronidazole (6 weeks)	Recovery
Spagnoli D, et al. 2003 [20]	<i>Gemella morbillorum</i>	API Gallery	None disclosed	Dental abscess	Cerebral abscess	Fever Confusion Headache Hemiparesis	Ceftriaxone Vancomycin (3 days) Amoxicillin/clavulanic acid (3 weeks) Ceftazidime (10 days)	Recovery
Messori, Anna, et al. 2002 [21]	<i>Gemella morbillorum</i>	API Gallery	None	None disclosed	Cerebral abscess	Fever Headache Lethargy Nausea Vomiting Photophobia Neck stiffness	Amoxicillin/clavulanic acid Clindamycin (6 weeks) Chloramphenicol (4 weeks)	Recovery
Martínez Beneito MP, et al. 2002 [22]	<i>Gemella morbillorum</i>	Not disclosed	None	Sinusitis	Cerebral abscess Osteomyelitis	Headache Nausea Vomiting Hemiparesis	Amoxicillin/clavulanic acid Cefuroxime Cefotaxime Tobramycin Metronidazole Vancomycin Ceftriaxone Metronidazole Vancomycin Ciprofloxacin Cefazolin Ceftriaxone and Ampicillin	Relapse after 13 days, Recovery
Murray, et al. 1998 [23]	<i>Gemella morbillorum</i>	Not disclosed	None disclosed	Septic arthritis caused by <i>G. morbillorum</i>	Cerebral abscess	Lethargy Fever Nausea Vomiting Neck stiffness Blurred vision/photophobia		Not disclosed
Tokuoka K, et al. 1997 [24]	<i>Gemella sp.</i>			Periodontitis	Meningitis	Neck pain Trismus Confusion		Recovery with apalic syndrome
Asensi V, et al. [25]	<i>Gemella morbillorum</i>	Not disclosed	None disclosed	Periodontitis	Cerebral abscess	Not disclosed	Imipenem (5 weeks)	Recovery

Table 1 (continued)

Article	Species	Means of identification	Morbidity factors	Potential favoring factors	Clinical presentation	Symptoms	Treatment (duration)	Outcome
Debast SB, et al. 1993 [8]	<i>Gemella morbillorum</i>	Not disclosed	None	Sinusitis	Meningoencephalitis	Headache Fever Malaise Confusion	Benzylopicillin Acyclovir	Death
Aspevall O, et al. 1991 [26]	<i>Gemella haemolysans</i>	API Gallery	Trigeminal neuralgia	Invasive neurological procedure	Meningitis	Fever Neck Stiffness Vomiting	Ampicillin (5 days) Cefotaxime (10 days) Benzylopicillin (4 days)	Complete recovery with no long-lasting effects
Garavelli, P L, et al. 1990 [27]	<i>Gemella morbillorum</i>		Not disclosed	Not disclosed	Meningitis		Ampicillin Chloranphenicol	Recovery
Mitchell RG, et al. 1985 [28]	<i>Gemella haemolysans</i>	API Gallery	Trigeminal neuralgia	Invasive neurological procedure	Meningitis	Fever Headache Neck Stiffness	Chloranphenicol Sulfadiazine	Recovery
This case	<i>Gemella</i> sp.	16S rRNA sequencing	ENT cancers		Meningitis	fever, confusion Neck Stiffness	Cefotaxime	Complete recovery with no long-lasting effects

To differentiate between pathogens for appropriate treatment and potential prophylaxis for close contacts in case of *N. meningitidis*, several multiplex PCR assays were performed. The BioFire FilmArray ME and QIAstat-Dx ME panels, which test for both *N. meningitidis* and *S. pneumoniae*, were negative. CSF antigen testing for *S. pneumoniae* (BinaxNOW, Abbott) was also negative. Blood and CSF cultures remained negative, likely due to prior antibiotic treatment. Consequently, the remaining CSF was sent to the Lille University Hospital Center for further analysis. Sequencing of the 16S ribosomal RNA identified the cocci seen on the Gram stain as a species from the genus *Gemella*, six days later.

The patient's condition improved with the resolution of the meningeal syndrome the day after appropriate antibiotic therapy initiation and the fever subsided 48 h later. The patient remained treated by Cefotaxime at a meningeal dose for seven days in a probabilistic manner, with an additional seven days after identification of the germ. CRP at discharge from hospital was 22 mg/l. The patient recovered without any neurological sequelae.

Given the discovery of an ENT germ responsible for the meningitis, an osteo-meningeal breach or ENT infection was suspected. A review of the initial cerebral CT showed no osteo-meningeal breach, sinus cavity infection, or bone lysis. A dental CT scan revealed a granuloma at position 42, with edentulism and poor dental hygiene but no bone lysis or secondary necrosis from laryngeal radiotherapy. Due to the high risk of osteonecrosis of the jaw, additional examination was not pursued as long as the patient remained asymptomatic.

Although no direct evidence could confirm the infection's origin from the ENT sphere, it is likely that the patient's history of ENT and esophageal cancers, along with recent radiotherapy and chemotherapy, promoted the infection's development. An infra-radiographic osteo-meningeal breach remains a plausible hypothesis.

The patient was readmitted a few months later with pulmonary lesions as well as several metastatic lesions attributed to his previously treated ENT cancers.

Review of the literature

As of writing this report, 22 cases of central nervous system (CNS) infections caused by various *Gemella* species have been reported with various clinical presentation, outcomes and laboratory findings. A comprehensive review is presented in Table 1. The cases were found using combinations of the keywords “*Gemella*, meningitis, nervous system infection, encephalitis, brain abscess, *Streptococcus morbillorum*, *Neisseria hemolysans*, case report” on pubmed.gov and google scholar with cases written in English or French from 1980 until 2022.

Out of the 22 cases, 59% of patients (13/22) presented with a clinical picture of meningitis and 41% (9/22) with

added encephalitis/brain abscesses. Complete recovery was obtained in 77% of cases (17/22), 9% (2/22) recovered with neurological damage, 9% (2/22) of patients had a fatal outcome, and in 5% (1/22) the outcome is unknown. Relapses occurred in 14% (3/22) of the cases with death resulting in 5% (1/22).

CNS infections caused by strains of *Gemella* spp. do not seem to be an emerging reality based on the various cases reported the past 40 years, as they appear to mainly affect immune-compromised adults with ENT and/or neurological breaches. In 64% (14/22) of cases, an underlying ENT or neurological breach was reported. That percentage increases to 93% (15/16) when only taking the cases with sufficient clinical background information into account. However, one pediatric case has been reported, as well as a few other cases in otherwise healthy adults with no apparent cause [10].

The outcome is usually very good with complete recovery, despite some cases with multiple relapses and death in the worst of cases, always following severe encephalitis with brain abscesses. An argument could be made that the (sometimes severe) underlying conditions of the patients could not only play a major role in the development of the disease but also the poor outcome.

The clinical presentation is usually typical of the affected sites, with fever headache and neck stiffness in cases of meningitis and added various neurological signs in cases with brain abscesses.

The treatment options were initially probabilistic, considering the patient's history (including penicillin allergy), and later adjusted based on the antibiogram when available, or clinical evolution, as highlighted in the review of the literature.

Discussion

We highlight in our case the difficulty that such unusual bacteria can pose and the usefulness of molecular microbiology, mainly the syndromic panels readily available in most laboratories, in allowing to quickly eliminate *S. pneumonia* and *N. meningitidis* as causing agents, therefore allowing unnecessary prophylactic and therapeutic measures to be avoided.

Furthermore, the 16S ribosomal RNA PCR and sequencing were especially useful in our case to identify the bacteria given the cultures remained sterile due to the antibiotic treatment, in highlight of the visible germ on the Gram staining indicating that there were indeed bacteria present in the CNS likely to be responsible for the symptoms.

Although meningitis caused by bacteria such as *Gemella* spp. appear to be milder than other bacterial meningitis, the mortality in the long run and risk of sequelae cannot be accurately predicted in light of the limited data available. In addition, the necessary

treatment and duration has never been evaluated and could benefit from comparative studies with a high level of evidence as shown by the various antibiotics used in the different cases, with modern microbiology being able to quickly identify the causing agents.

Abbreviations

CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
ENT	Ear nose throat
IV	Intra-venous
LP	Lumbar puncture
PCT	Procalcitonin
WBC	White blood cells

Author contributions

I.B. and L.J. wrote the manuscript. I.B. prepared the table. L.J. provided the clinical aspect. I.B. performed the review of the literature. E.M. overviewed the case and research. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The Clinical Research Ethics Commission (CERC) of Valenciennes Hospital met to examine the project entitled: Meningitis due to *Gemella* sp. in a patient with severe ENT conditions: case report and review of the literature Presented by Edith Mazars and gave a favourable opinion (Ref CHV-2023-014) after examining its conformity with the rules governing clinical research. (Date : December 20, 2023).

Competing interests

The authors declare no competing interests.

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