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Case Report

Insight review of the first surviving case of Ludwig's angina caused by Gemella morbillorum

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ABSTRACT

Our case report is presumably the second reported case of Ludwig's Angina caused by Gemella morbillorum and the first case reported that survived. We reviewed literature on Gemella morbillorum which is often a misunderstood microorganism but has the potential to cause serious infections and lethal complications in certain cases; its historical identification, characteristic features, advanced studies on its virulence, pathogenicity and other key information for identification. We also briefly reviewed the interesting details of Ludwig's Angina.

1. Introduction

We report our patient's clinical findings, investigations, treatment, post-operative progress making him the first surviving case. We wrote a literature review on Gemella morbillorum based on various cases reported, how it was first detected and through the years was transferred into various foster genera, till it was finally classified on phylogenetic characteristics in 2020; furthermore, its commensal behavior showing infections in immunocompromised/ immunocompetent individuals; as it has a strong affinity to integrate exogenous Deoxyribonuclease (DNA) by Horizontal Gene Transfer (HGT) by various speculations and we also give an account on Ludwig's Angina (LA).

2. Case Report

On January 28^{th} 2021, a 67-year-old male, presented to emergency department with classical features of LA with odynophagia for 7 days and one episode of high-grade fever the previous night; he had history of right 3^{rd} molar tooth extraction at a local dentist on January, 20^{th} 2021 following which there was painful swelling that gradually progressed to bilateral submandibular and submental region. A known case of type 2 Diabetes mellitus on combination of tablet Glimipride 1mg and Metformin Hydrochloride 500 mg twice daily post prandial for 15 years, also had Ischemic heart disease for which he underwent percutaneous transluminal coronary angioplasty 5 years prior and chronic hypertension for which he took tablet Amlodipine 5 mg once daily for past 5 years; with neither drug allergies nor addictions.

On examination, a diffuse, hard, tender swelling with erythema and local rise of temperature extending from submental and submandibular region 6cm x 5cm x 5cm from right to left angle of mandible and vertically extending till hyoid bone was found. Intraoral examination revealed trismus 2 finger breadth, right 3^{rd} molar extracted tooth socket appeared infected with obliteration of buccal vestibule due to intraoral

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dentoalveolar swelling with tenderness. Diagnosed with LA, he was planned for emergency incision and drainage (I&D) with adequate debridement of necrosed tissue under general anesthesia. Emergency investigations showed glycosylated hemoglobin level (HbA1c) 16.7, Random blood sugar 360 mg/dl, elevated serum creatinine level 2.39 mg/dl, Neutrophil count raised to 83.1% and total leucocyte count 16.8 x10^3/microlitre. However, respiratory rate, oxygen saturation, blood pressure and other vital parameters were stable. He was started on Inj. Regular Insulin subcutaneously with blood sugar monitoring and empirical treatment with broad spectrum antibiotics for aerobic and anaerobic microbes. Ultrasound of neck showed infected submandibular and submental region suggestive of cellulitis with no airway compromise.

Consent for surgery and emergency tracheostomy (if required during surgery) was taken. Under all aseptic precautions, with I&D 80-100 ml pus was drained and sample sent in a sterile screw-capped container immediately to Microbiology laboratory for culture and sensitivity.

A Gram's stained smear showed many pus cells and presence of Gram-positive cocci in pairs and short chains. Inoculated on 5% Sheep blood agar (SBA), MacConkey agar and Chocolate agar and incubated overnight at 37 ºcentigrade. After 2 days of incubation the colonies on SBA showed pinpoint to medium size colonies i.e. up to 0.5 mm in diameter, translucent, convex, smooth, circular, shiny and non-hemolytic colonies. Conventional Antimicrobial susceptibility test using Kirby Bauer's Disk diffusion method showed susceptibility to Gentamicin, Amoxicillin- Clavulanic acid, Piperacillin-Tazobactam, Ampicillin-Sulbactam, Imipenem, Meropenem, Cefoxitin, Ciprofloxacin, Levofloxacin, Cotrimoxazole, Vancomycin, Azithromycin, Clarithromycin, Erythromycin, Linezolid, Ampicillin, Amoxicillin and Benzyl Penicillin; suggesting Streptococcus genus, however, we wanted to identify at species level, so we used BD PHOENIX M50 ID and to our surprise found it to be Gemella morbillorum which is the second case reported in case of LA. Hence, it belonged to Gemellae genus rather than Streptococcus. Patient was started on intravenous Piperacillin + Tazobactam 2.25 gm thrice daily along with symptomatic treatment and inj. Regular insulin subcutaneously thrice daily according to blood sugar level monitoring. Subsequently his leucocyte count, serum creatinine levels and general condition improved. He was discharged on February 4^{th}, 2021 with medications including Tablet Faropenem 300 mg twice daily for 10 days to prevent recurrence. He continued Insulin Isophane / NPH and Human Insulin / Soluble Insulin-30/70 100 IU/ml Cartridge 3ml with blood glucose monitoring and antihypertensives. He was asked to follow up after 10 days to Outpatient department which showed his incision site had healed.

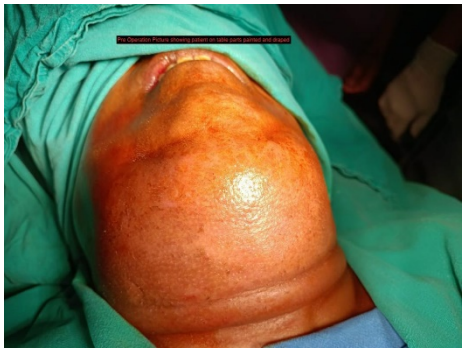

Fig. 1: Pre operation picture of patient with Ludwig's Angina

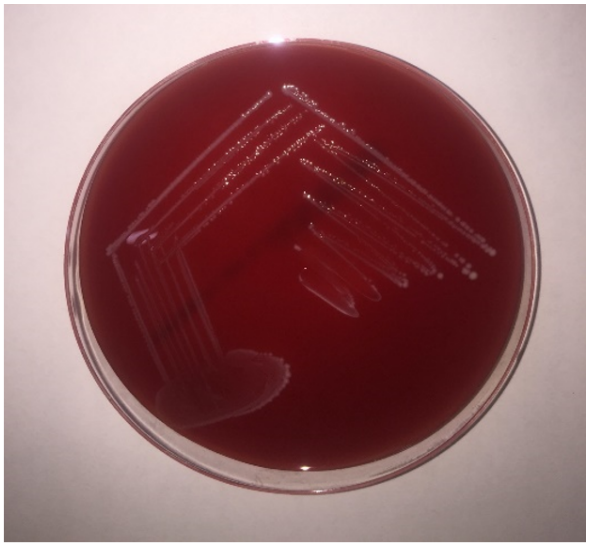

Fig. 2: Colonies of Gemella morbillorum after 48 hours of incubation at 37º C in 5% SBA

3. Discussion

G. morbillorum, a commensal in oral flora, after the tooth extraction at a local dentist and inappropriate antimicrobial treatment led to invading the tooth socket and infecting it and rapidly progressed to LA. Prompt diagnosis, rapid action to determine the causative organism with right antimicrobial therapy and adequate surgery saved further life-threatening complications.

Our literature review showed Gemella morbillorum has been classified according to NCBI Taxonomy in the year 2020 into Superkingdom: Bacteria, Phylum: Firmicutes, Class: Bacilli, Order: Bacillales, Bacillales Family XI. Incertae Sedis, Genus: Gemella, Species: morbillorum CC57F and morbillorum M424.[1] It is a Gram positive, Catalase negative, facultatively anaerobic, non-motile, non-spore forming coccus with variable arrangements as short chains, pairs or even singly present, which caused it to being thrust into different genera since its discovery in 1917; when Tunnicliff first isolated Gemella

morbillorum from a patient's blood sample who had measles and he named it as Diplococcus rubeolae until 1936.[2] It has relatively thin walls and can get decolorized so may show Gram variable tendency.[3] Prevot termed it as Diplococcus morbillorum which was modified in 1957 by Smith who suggested the genus Peptostreptococcus morbillorum in Bergey's Manual of Determinative Bacteriology, 7^{th} Ed. While in 1974, Holdeman and Moore transferred it to genus Streptococcus.[4]Hardie, in Bergey's Manual of Systemic Bacteriology, Vol.2 suggested that Streptococcus morbillorum could not be grouped with anaerobic streptococcus as it is aerotolerant and not strictly anaerobic.[4] So in 1988 Kilpper-Balz and Schleifer established a relationship of streptococcus morbillorum and Gemella haemolysans at a genus level based on physiological properties and studies of 16S Ribonucleic acid (RNA) cataloging and of Deoxyribonucleic acid (DNA) base composition (30 mol% guanine + cytosine) proved that Streptococcus morbillorum did not belong in genus Streptococcus but in genus Gemella as its biochemical, chemotaxonomic and physiological characteristics was closely related to Gemella haemolysans, hence it was termed as Gemella morbillorum.[4] A commensal in mucus membranes; in female genital tract, oropharynx and gastrointestinal tract. However, cases of severe localized and generalized infection were observed more so in patients with co-morbidity or in immunocompromised state,[2] where it causes opportunistic infection like necrotizing fasciitis.[5] Gemellae can cause a range of infections varying in anatomical sites, the severity of the disease and despite previous speculations in immunocompromised/ immunocompetent individuals. Termed as a "PATHOBIONT" which means in relation to its complex bacteria-host interaction it can either show pathogenic or commensal behavior.[6] Reports have shown Gemella morbillorum as pathogen in infective endocarditis cases,[7] A review study done in 2019 showed out of 66 cases of Infective Endocarditis caused by Gemella genus 34 were caused by Gemella morbillorum.[8] Reports on sepsis,[9] cases of peritonitis,[10] Septic arthritis,[11] central nervous system infections[2] have shown the wide spectrum of serious infections that it can cause. There may also be a direct correlation of occurrence of colorectal cancers and abundancy of Gemellae in the stool of the patients as compared to healthy individuals; there was increase in amount of Gemellae in the cancer tissue as well in patients of colorectal malignancies.[12] This may suggest a dysbiosis with G. m. colonising acting as a predisposing factor for colorectal cancer and more studies should be encouraged on this for premalignant determination of colorectal cancers based on microbiome.

In 2005, the only reported case of LA due to Gemella morbillorum that we searched in PubMed and Google Scholar ; where a 48-year old immunocompetent male developed LA with mediastinitis where Gemella morbillorum was detected as the causative organism and despite best efforts the patient could not be saved and passed away after 12 days of rigorous treatment.[13] In various cases reported mainly four most common pathogenic species of genus Gemellae: G. morbillorum, G. haemolysans, G. sanguinis, G. bergeriae; G. morbillorum and G. haemolysans are most common pathogenic species; out of which G. morbillorum causes twice as much infections than G. haemolysans. Advanced methods used to detect G. morbillorum are Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), BD PHEONIX M50 ID and whole-genome sequencing (WGS) analysis. The first sequence produced for Gemella was in 2008. Since then WGS analysis has proven to be far superior method to identify rare bacteria and impart a clearer picture about their transmission events.[14] The virulence and pathogenesis depends on various factors and comparisons of proteomes of different species of Gemellae provided an insight, as G. morbillorum unlike G. haemolysans lacks the capsular gene cluster which is required for encoding capsular polysaccharide which aids in evading the opsonophagocytic process, however the presence of phosphorylcholine-containing teichoic acid and choline-binding proteins have been found in the Gemellae genus which increases the adherence of the bacteria to the host cell by binding to the receptors of platelet-activating factor; beta-haemolysin toxins are found in many species of Gemella except G. morbillorum while different species may show alpha-haemolysis, beta-haemolysis or no haemolysis depending on horse or sheep blood and the agar used; G. morbillorum and G. haemolysans both have exclusive Fibronectin-collagen binding- T antigen protein which facilitates adherence to adhesive matrix molecules that are present on host receptors and damaged tissues indicating a HGT from streptococcus oralis having the similar surface component ; also an important peptidase_S8 and Fn3_5 domain fusion present in G.morbillorum, G. haemolysans and G. sanguinis is responsible for effecting the complement C5a and Interleukin-8 resulting in spread of soft tissue infection and formation of pus; G. morbillorum and G. haemolysans possess a Near iron transporter domains that seize heame containing molecules and use the iron as cofactors and further accentuate the invasiveness of the disease.[6] The potential of G. morbillorum to undergo HGT and assimilate exogenous DNA to atone for its incompetent genes so as to escalate its virulence renders a possibility to emerge as a possible super bug that can develop antimicrobial resistance that requires sophisticated methods for detection.

Our review on LA showed it was first described by Wilhelm Friedrich Von Ludwig in 1836, who was the president of Württemberg Medical Association and the chief physician of the royal family; ironically when he was 75

years old he passed away after few days of infection in his neck, it is still an unsolved mystery weather Ludwig succumbed to the illness he himself described.[15]

LA is a rapidly progressive gangrenous cellulitis or necrotizing fasciitis involving the submandibular, sublingual and submental spaces and can spread further to mediastinum.[16] It spreads rapidly to pharyngeal and laryngeal airways and can cause deep cervical fasciitis and spread to epiglottis causing airway compromise.[17] Hence to prevent life threatening conditions like airway obstruction, septic shock or empyema, early surgical intervention and appropriate antimicrobial therapy could prevent fatality.[16,18] Mortality rate from LA is 8%[19] Streptococcus species is most common organism isolated, other causative organisms are Bacteroides species, Micrococcus species, Fusobacterium species and Peptostreptococcus species.[16] The most common etiological cause is odontogenic in nature, infection in subgingival pocket spreads to floor of mouth, into submandibular and submental spaces,[17] However lymphatic involvement is seldom seen.[20]Other etiologies like injury to the floor of mouth, mandibular fractures, oral piercings or lacerations, peritonsillar abscess, parapharyngeal abscess, infected thyroglossal cysts, submandibular sialadenitis have also lead to LA.[16,17] Steroid therapy, hepatorenal dysfunction and diabetes mellitus, colorectal diseases, dental procedures can also act as predisposing factors.[21]

4. Conclusion

In our case we identified Gemella morbillorum but would not be surprised if this organism goes undetected in many cases of LA. With conventional methods it is often underreported and misidentified as viridans group of streptococci or other related cocci.[22] So instead of suspecting routine micro-organisms as causative agents to LA we should identify the microbe accurately, to understand its host-bacteria interaction and its role as normal flora in immunocompetent/ immunocompromised cases. Case reports of this rarely detected organism should be encouraged to collaborate findings of its effects on various systems, so that we can understand better our mysterious and mischievous Gemella morbillorum.

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None.

6. Conflict of Interest

None.

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