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RESEARCH ARTICLE

Osteonecrosis of the Jaw Related to Tuberculosis and Concomitant Infection with Plasmodium Ovale Wallikeri: A Summary

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ABSTRACT

In 2012, a retrospective case report of 60 cases of extreme osteonecrosis in the maxillofacial region collected over a 3-year period, was published. The cases presented in 2 groups. One group showed grey-like necrotic bone, and the other group which was much more plentiful, had swelling and pus draining fistulae associated with the osteonecrosis.

A further prospective study of 19 patients collected over a 3-month period was analysed and indicated tuberculosis to be the cause. All 19 cases presented with mandibular lesions. Orofacial tuberculosis is known to be rare.

Further studies of the clinical samples with amplified DNA and sequencing, provided direct evidence to support the conclusion that a combination of Mycobacterium tuberculosis, Plasmodium ovale wallikeri and oral bacteria are involved in this particular type of maxillofacial destruction.

Further studies are planned to elucidate the cause of the "greyish" necrotic bone documented in the paper from 2012.

Introduction

The Mercy Ships, a voluntary medical aid organization, provided free treatment in the West African countries Libera, Togo and Benin in 2008-2010. About 23 000 individuals sought treatment in this time span. A group of clinicians noticed how some of these exhibited unusually aggressive osteonecrosis of the jaw (ONJ), and published a paper documenting sixty cases.[1] The West African population may be at increased risk for infections and disease due to inadequate access to vaccination programmes and health care. The prevalence of the observed ONJ (0.26%) was likely to have been higher, as frail and ill patients may not have been able to travel for days or did not seek treatment due to silent lesions or lack of information.

The sixty patients spanned a wide age range of 5 to 85 years of age. The median age was 35.5 years and a male:female ratio of 1:1.5. Thirty of them had intraorally exposed bone and one with extraoral exposure. The mandible was affected among 54 patients, whereas the condylar head was affected in 11 of these. The mandibular angle was involved in 15 cases. Almost half of the cases, 27, had an extraoral fistula. Mainly two distinct manifestations of ONJs could be identified based on clinical examinations. The most prevalent manifestation typically consisted of unilateral facial swelling, persistent extra- or intraoral fistulae, and osteolysis of the jaw (figure 1). The second manifestation was characterized by necrotic "greyish" sequestra, without swellings or sinus tracts (figure 2).

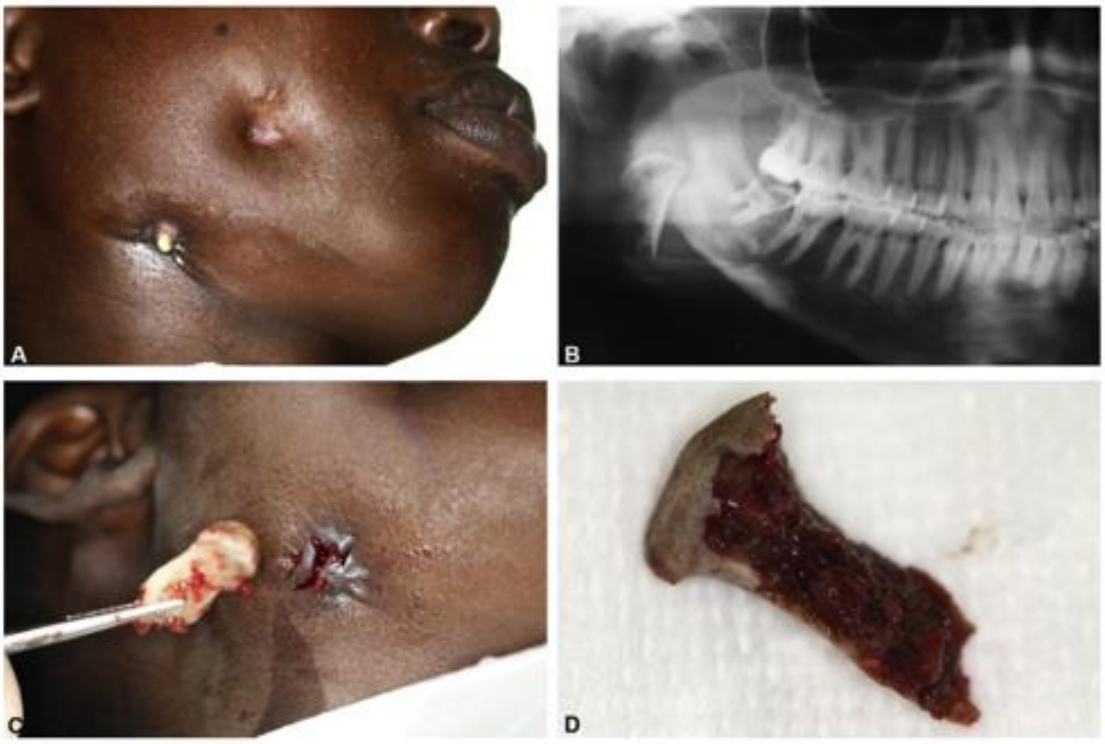


Fig. 1. A female, 22 years, with right-sided swelling with draining extraoral fistulae (A). Right condylar head with a "floating" appearance on the panoramic radiograph, and a decayed lower third molar (B). The condylar head was extracted through the fistula (C), and exhibited severe osteonecrosis medially.[1]

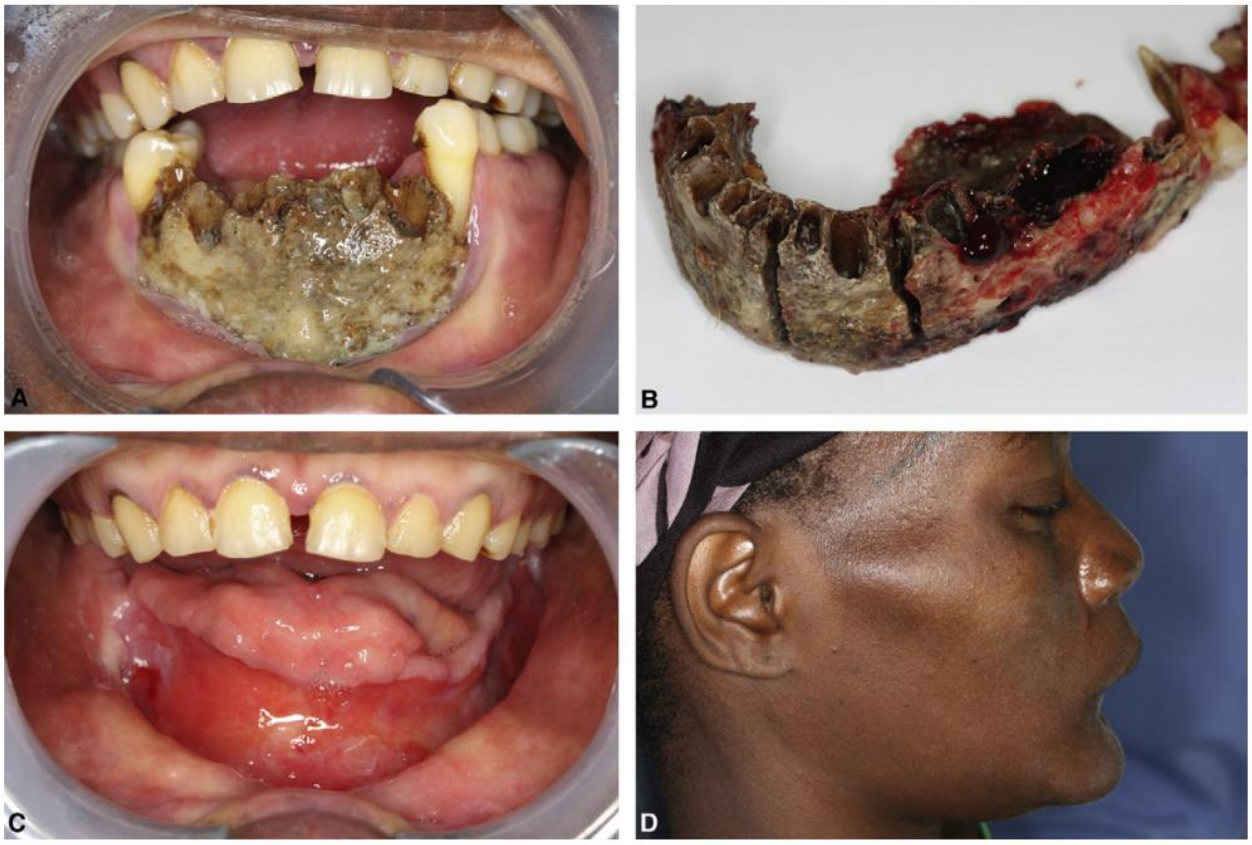


Fig 2. Initial presentation of a woman at 40 years of age, with apparent osteonecrotic mandibular sequestra (A). The sequestra post-removal (B). Uneventful intraoral healing (C). Gross swelling or fistulae were non-present at presentation. After complete healing, the lower mandibular rim remained, and the patient accepted an intraoral prosthesis.[1]

All sixty patients were in need of invasive treatment, including dental extractions, debridement and/or sequestrectomy, in combination with antibiotics. Osteolysis to such extents can result in compromised chewing ability and facial disfigurement, which were evident in many patients postoperatively. The drastic bone destruction as described in these sixty cases is unusual. Similar destruction of the jaw is more commonly observed in cherubism, odontogenic tumours or cysts, malignancy or orofacial tuberculosis.[2] This paper serves as a summary of a series of studies conducted to elucidate the aetiology behind the sixty cases' extreme osteonecrosis.

Hypotheses

ONJ may be initiated by a variety of causes. In the Western world, medications are among the most well-known culprits. Since the first report of medication-related ONJ in 2003[3,4], medications used to effectively treat osteoporosis and prevent skeletal metastasis in cancer patients have been established as risk factors. Such medications were inaccessible to the sixty patients.

In the 19th century, phosphorous necrosis of the jaw, nicknamed "phossy jaw", was linked to the match making factories' utilisation of white phosphorous[5]. Another occupational disease related to ONJ was the so-called "radium jaw". The painters of luminous dials were particularly affected as they used to lick the bristles, inadvertently ingesting radium.[6,7] Today, these occupational diseases are regarded to be extinct.[8] It is unknown if this region involves any environmental or industrial propensity for these conditions.

Ten to twenty-five percent of West Africa's population is thought to have sickle cell disease,[9] a common coagulopathy. Coagulopathies have been reported to cause avascular osteonecrosis as a consequence of thrombus formation in the intraosseous microcirculation.[10-13] With 1.6 million new cases every year, tuberculosis (TB) is another illness that is regularly encountered in the region.[14] Pulmonary TB is most prevalent, although 20% of cases are extrapulmonary and may involve several organ systems,[15] such as the skeletal system in 35% of cases. Although extremely uncommon, gingivitis or dental caries might cause TB to involve the maxillofacial region[16-18] by dissemination of the Mycoplasma tuberculosis-bacterium from the infectious focus. Only 13 of 42 casesof orofacial TB, according to Mignogna et al., were related to an oral infection.[19] Orofacial TB, or rather maxillofacial TB, may affect several tissues in addition to the bones, such as the head and face, the gingiva, tongue, masticatory muscles, and buccal mucosa, salivary glands, lymph nodes, among others.[20]

In 2012, Andrade and Mhatre,[20] published a report of 46 cases of orofacial TB, collected over 16 years in India. Some of these cases presented with involvement of the mandibular angle and ramus, with or without intraoral or extraoral draining fistulae, resembling the sixty cases by Khullar et al.[1] Patients with TB of the temporomandibular joint (TMJ) were documented by Patel et al.[21] and Hebling et al.[22] among African immigrants in Europe. However, a patient from India with TMJ-TB was reported by Ranganathan et al.[23] As the reports of orofacial-TB closely mirrored the clinical findings among the sixty cases, Khullar et al. considered tuberculosis to be a possible cause worth further investigation.

Testing the hypothesis

Over a 3-month period in 2011, 19 patients attended Mercy Ships dental clinic in Sierra Leone and Trinity Dental Clinic in Liberia for complaints of unilateral facial swelling and pain. Many of them with draining fistulae. Clinical and radiographic examinations revealed mandibular ONJ, mainly affecting condylar heads, akin to the first set of symptoms described among the sixty cases.[1] It should be noted that their neighbours and family members reportedly had similar complaints. Eleven of the patients also reported lethargy and fever. All patients received surgical management for their orofacial complaints as indicated, and discarded surgical debris (soft and hard tissues) was stored in 10% formaldehyde. In collaboration with an experienced team of researchers, the samples were sent for further analysis in a university research lab.[24]

Analysis consisted of micro-computed tomography (micro-CT)(MicroXCT-200; Zeiss), histology (haematoxylin and eosin stain, H&E) and immunohistochemistry. The latter utilised antibodies for EMR-1 (PA5-33502; Thermo Fisher Scientific, MA, USA), to identify mature macrophages, and antibodies (GWB-EF714E; GenWay Biotech Inc., CA, USA) to detect M. tuberculosis-derived proteins. Micro-CT showed a destruction pattern characterized by a pitted cortical surface (Fig 3). Histological staining revealed inflammation with extravasation of red blood cells accompanied by a large number of blood vessels, macrophages, and signs of osteoclast activity (Fig. 4). Immunohistochemistry with EMR-1 identified several positively stained cells, confirming the presence of mature macrophages. Antibody staining of M. tuberculosis-derived proteins indicated the presence of the bacterium with several positive round and rod-like structures (Fig. 4). The findings support the presence of M. tuberculosis in microbial invasion and possible macrophage and osteoclast hyperactivity.[24] It must be noted that DNA was isolated from a small number of samples and additional polymerase chain reaction (PCR) showed the presence of IS6110 and MPB64 genes. The genes function as a diagnostic marker for TB[25] and strengthens the conclusion that TB was involved in the ONJ reported among the sixty cases.[1] DNA sequencing of the involved patients was regarded necessary to characterise the strains and understand the pathophysiological mechanism.

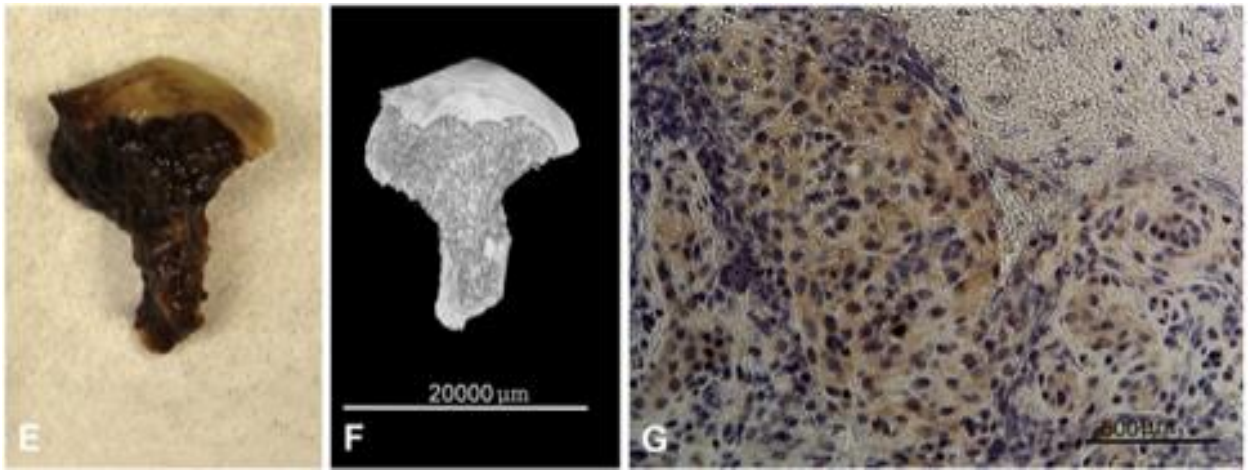


Fig. 3. Part of surgically removed condylar head, its medial side shows bone lysis (E). Pitted-destruction pattern, by micro-CT (F). EMR-1 antibody-stained macrophages (purple)(G).[24]

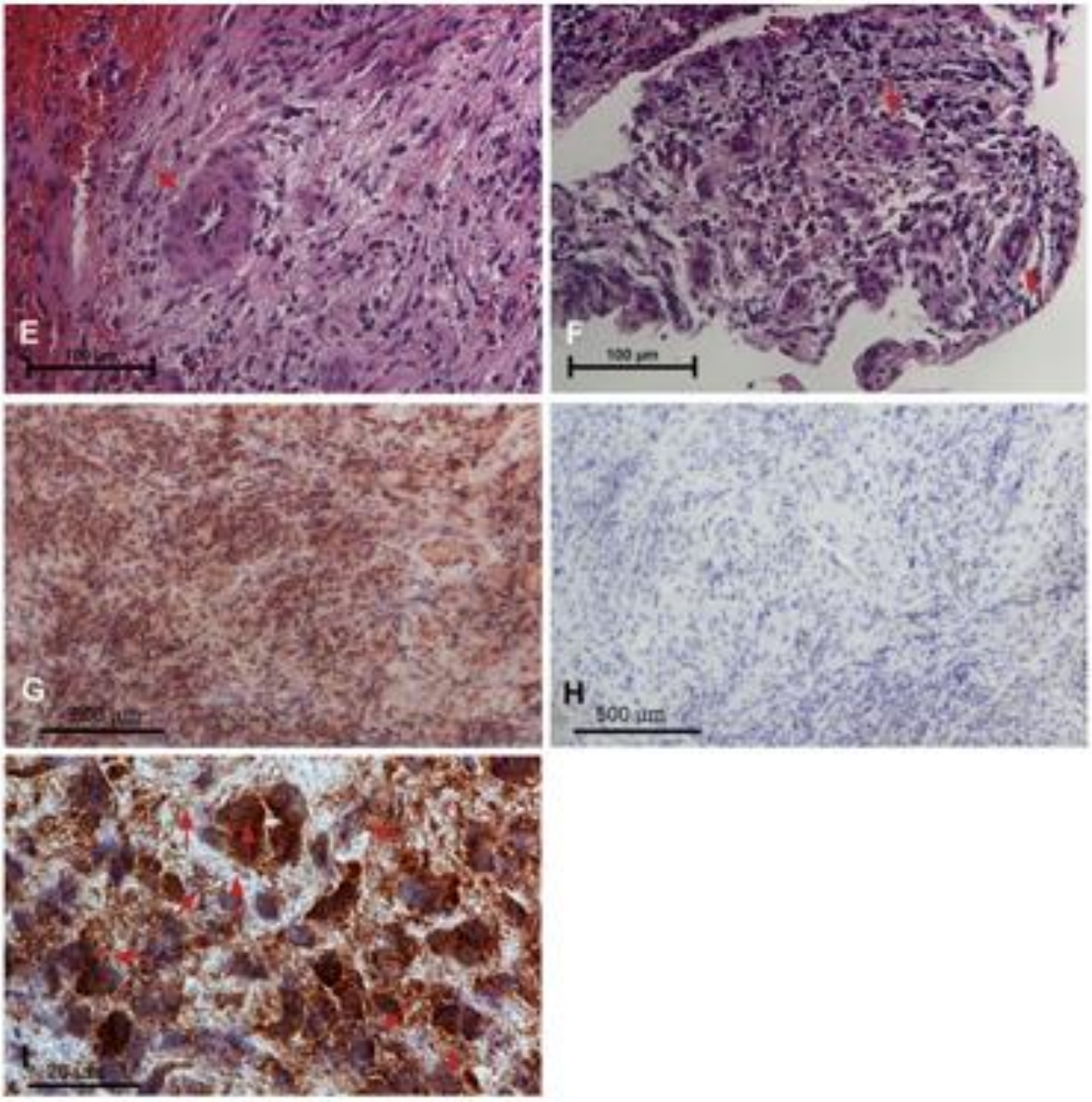


Fig. 4. Condylar head with medial bone destruction. H&E staining shows a thick blood vessel (arrow) and extravasated erythrocytes (E). H&E staining shows inflamed tissue with macrophages, numerous thick blood vessels and erythrocytes (F). EMR-1 positive macrophages (G) and a negative control-antibody (H). Several round and rod-like structures (arrows), stained by antibody against M. tuberculosis-derived proteins, surrounding macrophages (I).[24]

Validating the hypothesis

Nine of the nineteen patients (Table 1) included in the previous study[24] were included for bacterial genome sequencing. To achieve that, DNA extraction from their formaldehyde-fixed tissue samples, followed by amplification and metagenomically analysis had to be performed.

DNA extraction was performed using the CryoPrep (Covaris, Inc.) extraction system and an extraction kit (Sigma-Aldrich). By placing samples on electrophoresis gels, it was possible to ensure that the extracted DNAs were of high quality and had not degraded. Following PCR, the resulting sequence libraries were diluted, and samples were tested for quality using a DNA high sensitivity chip bioanalyzer. The Harvard Medical School's biopolymer laboratory performed next-generation sequencing. DIAMOND v0.9.26 was utilised to align reads to the NCBI-nr database and MEGAN 6 for taxonomy binning to analyse the whole-genome sequencing data of the nine samples that contained both microbial and human DNA.[26,27]

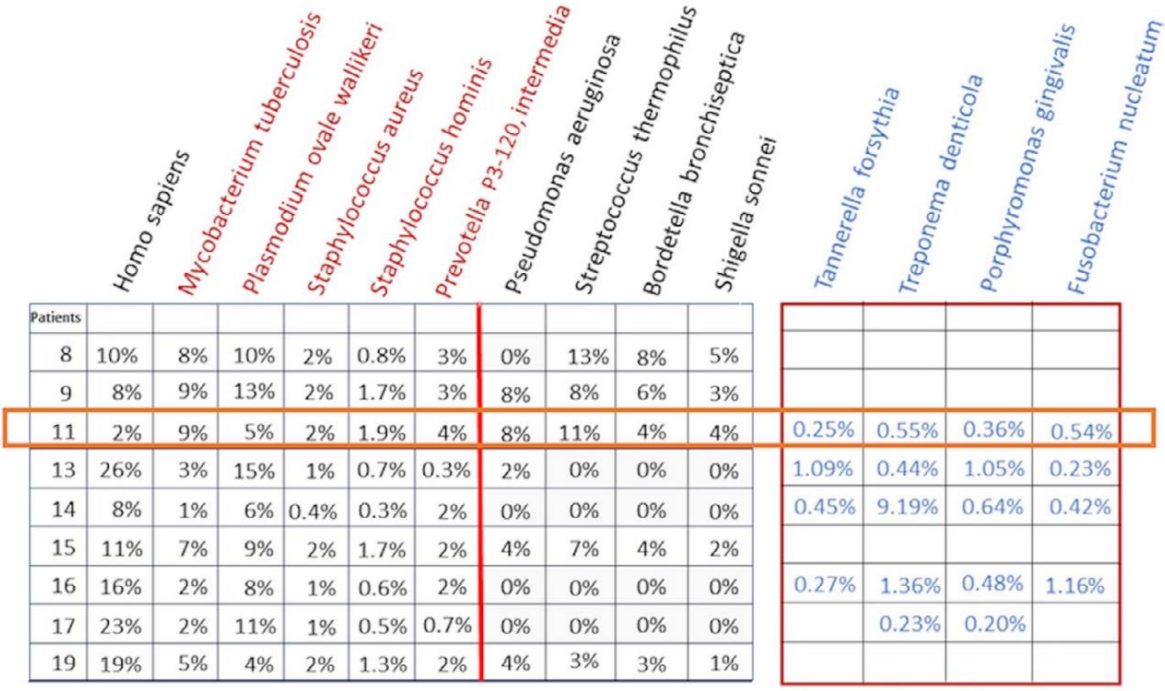
Patient Number (Khullar et al., 2016)	Gender	Age at presentation	Specified mandibular location
8	M	32	Anterior mandible
9	M	41	Right ramus/ coronoid
11	F	70	Left body
13	M	42	Right ramus/condyle
14	F	22	Right body/ramus/ condyle
15	M	17	Left body/ramus/ condyle
16	F	21	Bilateral body
17	F	27	Bilateral body/ condyle
19	F	30	Right body

Table 1. The respective patient identification numbers, genders, ages at presentation and the tissue samples' mandibular locations available for DNA extraction.[2]

The resulting sequencing revealed that several bacterial and other sequences were present, in addition to Homo sapiens. The most prominent sequences present in all nine individuals were Mycobacterium tuberculosis, Plasmodium ovale wallikeri, Staphylococcus aureus and hominis, Prevotella P3-120, and intermedia (Fig. 5).

Yang et al.[2] analysed the quantities of the TB-causing M. tuberculosis and the parasitic protozoa causing malaria, Plasmodium ovale wallikeri, DNAs in order to speculate on the probable roles that the various bacteria may have had in the destruction of jaw bones, they discovered that all but patient 11 could be divided into two groups. The M. tuberculosis

DNA levels in Group 1, which included patients 13, 14, and 16 and 17 with ages ranging from 21 to 42 years, were 1% to 3%. M. tuberculosis levels in Group 2 were between 5% and 9% among patients who were 8, 9, 15, and 19 years old and had ages ranging from 17 to 41. Staphylococcus aureus/hominis DNA levels were compared to M. tuberculosis DNA levels in Groups 1 and 2, and tissues from Group 2 patients had the greatest amounts of both. Plasmodium ovale wallikeri DNA was at a relatively low level (4%), whereas M. tuberculosis DNA was among the highest amounts found in tissue from patient 11. Co-infection of malaria and TB is exceedingly rare, and has a reported prevalence of 2.2%.[28] The co-presence of M. tuberculosis and Plasmodium ovale DNA is therefore of particular interest, and poses the question of whether their interaction may have played a significant role in the severe ONJ.



Patients	Homo sapiens	Mycobacterium tuberculosis	Plasmodium ovale wallikeri	Staphylococcus aureus	Staphylococcus hominis	Prevotella P3-120, intermedia	Pseudomonas aeruginosa	Streptococcus thermophilus	Bordetella bronchiseptica	Shigella sonnei	Tannerella forsythia	Treponema denticola	Porphyromonas gingivalis	Fusobacterium nucleatum
8	10%	8%	10%	2%	0.8%	3%	0%	13%	8%	5%				
9	8%	9%	13%	2%	1.7%	3%	8%	8%	6%	3%				
11	2%	9%	5%	2%	1.9%	4%	8%	11%	4%	4%	0.25%	0.55%	0.36%	0.54%
13	26%	3%	15%	1%	0.7%	0.3%	2%	0%	0%	0%	1.09%	0.44%	1.05%	0.23%
14	8%	1%	6%	0.4%	0.3%	2%	0%	0%	0%	0%	0.45%	9.19%	0.64%	0.42%
15	11%	7%	9%	2%	1.7%	2%	4%	7%	4%	2%				
16	16%	2%	8%	1%	0.6%	2%	0%	0%	0%	0%	0.27%	1.36%	0.48%	1.16%
17	23%	2%	11%	1%	0.5%	0.7%	0%	0%	0%	0%		0.23%	0.20%	
19	19%	5%	4%	2%	1.3%	2%	4%	3%	3%	1%				

Fig. 5. All nine patients shared percentage levels (in black) of DNAs from Homo sapiens to Prevotella P3-120, intermediate; some patients shared percentage levels (in blue) of DNAs from Pseudomonas aeruginosa to Shigella sonnei; and some patients shared percentage levels (in black) of Tannerella forsythia to Fusobacterium nucleatum; empty boxes indicate that DNA was not detected. The germs in the illustration were all coated with DNA from patient 11 (whose frame is delineated by red lines).[2]

Discussion

Humans are P. ovale wallikeri's natural host, once transferred through a mosquito bite, the parasitic protozoa will reproduce in the liver. From there, parasites will spread to the systemic circulation where red blood cells become infected. Coagulopathy and destruction of both infected and non-infected

red blood cells may follow, with a range of accompanying clinical symptoms.[29-31] The malaria caused by P. ovale wallikeri is seldom of the severe or lethal kind, but is reportedly endemic in West Africa.[32] A possible explanation of the malaria-TB co-infection mechanism behind the extreme ONJ could involve P. ovale wallikeri's disruption of capillaries, similar to avascular osteonecrosis by sickle cell disease, in M. tuberculosis-infected jaw bone. Interestingly, P. falciparum, which commonly causes severe malaria, may augment a mycobacterial infection.[33] P. ovale comprises two strains, wallikeri and curtisi, which are genetically unique.[34] A strain-specific host-immune response cannot be excluded, P. ovale wallikeri may very well specifically exacerbate bone lysis with TB as none of the samples contained the curtisi strain. The ONJ may have begun with M. tuberculosis infiltrating the mandible through the lymphatic or hematogenous system. The condyle has a profound blood supply compared to the rest of the mandible and could have provided as entrance.[35-38] The local capillary build-up of P. ovale-infected red blood cells may have been made possible by periodontal inflammation. The local conditions would have promoted avascular osteonecrosis due to coagulopathy in an otherwise poorly vascularised organ as the mandible. The P. ovale-exacerbating effect in the presence of M. tuberculosis would have set the stage for aggressive bone destruction. However, the presence of other bacteria in the analysed samples may also play a role. The greatest quantities of M. tuberculosis DNA and moderately high S. aureus DNA levels were found in Group 2 and Patient 11, respectively. An analysis employing the Pearson correlation coefficient (p=.000588, r=0.913) supports this. Finally, the Pearson correlation coefficient (p =.00112, r = 0.895) is supportive of a link between the amounts of DNA from Prevotella species in all fragments and the amounts of M. tuberculosis. Prevotella species may therefore be important contributors. These findings support the hypothesis that S. aureus and Prevotella species may have sped up the deterioration of the mandibular bone. S. aureus, which makes up 20-50% of the population's microbiota, may enter blood vessels after the epithelial barrier has been breached, attach to exposed vulnerable surfaces, and collaborate with M. tuberculosis in the destructive bone process. S. aureus may infiltrate osteoblasts and osteocytes, where it can live long periods, by binding to fibronectin in the extracellular matrix and integrins on cell surfaces. Both *in vitro* and *in vivo* studies have been conducted on S. aureus' behaviour of cell infiltration.[39,40] The bacterium can also promote osteoclast formation by expressing a number of proteins, such as NFATc1, RANKL, MCSF and the MCSF-receptor,[41,42] and may contribute to apoptosis of both osteoblasts and osteocytes. This may explain the vacant bone lacunae identified in the histological sections by Khullar et al.[24]

Future directions

Since 2008, Khullar et al. have collected and analysed material from a group of patients, from Liberia, Benin and Togo, with unusually severe ONJ.[1,2,24] Most of the patients

presented unilateral facial swelling, draining fistulae, and extensive bone destruction of the jaw. The series of studies published by the authors is illustrative of how clinicians and researchers can cooperate to develop novel knowledge about diseases or conditions. Still, several aspects remain to reach a conclusion. The reported ONJ is aesthetically debilitating, reduces the chewing function and quality of life, and the epidemiological extent is unknown. The current material does not explain why the patients' jaw bones were affected rather than other skeletal structures. TB-involvement of the vertebrae and long bones are far more prevalent.[43,44] The lack of Plasmodium ovale curtisi cannot be explained by the current material either. Future directions should focus on elucidating the following mentioned aspects in order to fully understand and prevent the development of the condition.

Furthermore, in the report of the sixty cases,[1] another manifestation of ONJ was described. A severely necrotic "greyish" bone sequestra similar to the historical "phossy jaw". This ONJ was not associated with fistulae or swellings. Further studies are planned to elucidate the cause.

Conclusion

A retrospective case report of extreme osteonecrosis of the jaw, was published in 2012. A further prospective study indicated tuberculosis to be the cause. Direct evidence obtained by DNA extraction and sequencing supported the conclusion that a unique combination of Mycobacterium tuberculosis, Plasmodium ovale wallikeri and oral bacteria are involved in this particular type of osteonecrosis of the jaw.

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Competing interests
The authors disclose no conflict of interest.

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