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Historical Pathologica

A 20th century case of noma infection following typhoid fever from the Morgagni Museum (Padua, Italy)

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Summary

Noma is a potentially fatal, gangrenous disease that leads to tissue destruction in the face. It has been proven to develop mostly in children living in extreme poverty.

There is a lack of data regarding microbiological analysis of the ulcers, making the knowledge of the bacteria involved and its etiology still unclear. Within this framework, pathological specimens from museological collections could offer relevant improvements for the comprehension of etiology of noma. The Morgagni Museum of Human Anatomy in Padua hosts a unique case of noma dating back to 1902, and two related specimens, a mesenteric lymphatic ganglion and a spleen.

The bacteriological analysis of the Museum's case showed the presence of Typhus bacilli in the patient's cheek and led to hypothesize the correlation between typhoid infection and noma.

The specimens coming from historical collections may lead to better knowledge about etiology of noma, and potentially prevent its invalidating sequelae.

Key words: Noma, Cancrum oris, Thyphoid fever, Museum collection, Bacteriological analysis

Introduction

Noma (or Cancrum Oris) is a gangrenous disease that leads to severe tissue destruction in the face and it is associated with a high mortality rate, estimated at 90% in children[1]. It has been proven to develop mostly in young children living in unsanitary conditions and extreme poverty. The etiology of Noma is still unknown, although it seems to be related to malnutrition, compromised immune system, poor oral hygiene, dentition period, and it is triggered by an unidentified bacterial factor. Noma mostly affects children in sub-Saharan regions of Africa; many cases have also been described in Latin America and in Asia.[1]

The evolution of the disease is very rapid: the first sign of Noma is a unilateral edema of the cheek and gingiva. The necrotic process spreads to the mucosal surface of the cheek and eventually to the bone structures of maxilla and mandible. The unmanaged infection can cause death only a few days after the onset of edema, generally because of starvation and sepsis. If the disease is detected at an early stage, noma can be healed. However, due to delay in seeking medical care, the patients' scars often lead to definitive stricture of the mouth. Moreover, the disease tends to be neglected by the scientific community and the resources and preventive strategies in the treatment of noma still need to be implemented.[2]

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History of Noma

Although most of the descriptions of the disease date back to the 19th century, Noma was already known by Ancient Greeks, who reported the first cases of the illness.

Early descriptions of similar clinical conditions were made by Hippocrates (460-370 BC) and Galen (129-200 AD), although the disease was not fully understood or properly described [3].

The first clear description of Noma was given by Carlous Battus in 1595 (Xhandboeck der chirurgjien), who reported cases of a rapidly spreading, corrosive ulceration of the mouth in children. In his description he uses the term "cancer", as defined by Celsus.[1]

Later in 1680 Cornelis van de Voorde (1628-1686), a Dutch surgeon, was the first to use the Greek word "Noma" to describe a fast-spreading ulceration in wet soft tissues in children, mostly happening in the mouth [4].

Finally, the first proper definition of noma was given by Jules Tourdes (nd) in 1848 and it still applies today. In his dissertation "Noma, or sphacellum of the mouth in children" he describes the pathology as "a gangrenous disease affecting the mouth and face of children living in poor hygiene conditions and suffering from debilitating diseases, especially eruptive fever, beginning with an ulcer on the oral mucosa rapidly spreading outside and destroying the soft and hard tissues of the face-and almost always fatal" [5].

During the 18th century, both in the Netherlands and in Great Britain, research regarding Noma brought to a better definition of its etiology. Relevant analyses regarding the pathology were carried out by the Norwegian Gabriel Lund (1773-1832), who attributed the onset of the infective disease to poverty and malnutrition among children [6].

In the same decades, the British doctor John Addington Symmonds (1807-1871) was the first to confirm the relationship between measles and the consequent onset of the necrotic lesion on children's cheeks [6].

From that period on, the research about Noma focused on the significant connection with previous or concurrent infectious diseases. A fundamental impact was given by the newest bacteriological discoveries, that brought the focus of the studies on the microorganisms colonizing the ulcerative lesion.

Noma proved to be mostly related to measles, malaria, tuberculosis, small-pox and typhoid fever, as proved by the copious cases reported during the 19th and 20th century.

In particular, many underlined the correlation between the onset of noma and previous infection with typhoid fever, caused by salmonella bacteria.

Hermann Lebert (1813-1878), professor of Clinical Medicine at the University of Zurich, analyzed the consequences of the endemic typhoid infection that erupted in 1854 in Canton Zurich. He underlined the appearance of noma lesion on the check of an 8-year-old female patient, who contracted typhoid fever a month earlier. The author could not explain the pathogenetic evolution of the disease [7].

Curt Schimmelbusch (1860-1895), director of the Berlin Polyclinic, reported the case of noma in a 5-year-old female patient who was affected by typhoid fever. After further analysis, the author described how the central and peripheral area of the ulcer were sharply different microscopically with no gradual development of the necrotic process. Curt Schimmelbusch did not specify if the microorganisms found in the noma lesion were typhus bacilli. The Eberth bacillus (also known as Salmonella enterica ser. Typhi) was found in the ileum, but not in the spleen, liver or kidneys [8].

Rudolf Matzenauer (1869-1932), Professor at the University of Graz, also described cases of noma after typhoid infections. He underlined that many exanthematic diseases such as Typhus, Measles and Scarlet Fever may possibly put at risk for infections and noma [9].

Antonino Longo, (1874-1943), Italian pediatrician, studied the onset of infectious disease in children, such as tuberculosis, diphtheria and meningitis. In 1904 he analyzed two cases of noma and focused his research on the bacteriological species colonizing the ulcerative lesion. He observed that the microorganisms may vary in different patients, showing that an important role in the evolution of the disease is related to the intrinsic conditions of the child and its bacterial flora. Furthermore, he hypothesized that the major role in the etiopathogenesis of noma is related to cytolysins resulting from the preceding infectious disease [10].

Albert Eckstein (1891-1950), a German doctor who immigrated to Turkey, described many cases of noma that he studied himself. Contrary to what was reported by other previous and contemporary authors, Eckstein observed a prevalence of noma after measles infection. Only two of 40 cases of noma were associated with typhoid infections. Furthermore, he asserted that "In only a few of the cases was there any tendency to cachexia or atrophy, which is contrary to claims of most other authors. Most of our patients showed a normal or strong degree of nourishment and health"[11].

Michael Tempest (1921-1995), Plastic Surgeon at the University Hospital College of Wales in Cardiff, thoroughly studied the factors predisposing to noma disease. The author explained that the ulcerous lesion appears during the convalescence of infectious diseases such as measles, malaria, typhoid fever, tuber-

culosis, with different trends in time. The association between noma and other co-infections often followed climatic changes and the endemic illnesses of a specific area. Michael Tempest also described Borrelia vincentii and Fusiformis fusiformi as being the microorganisms mostly found in the ulcer [12].

Finally, in the most recent descriptions of noma cases, the authors assert that the disease is nutritionally acquired immune deficiency syndrome, confirming the previous literature.

The pattern of noma has been described by S.A. Adeniyi and K.J Awosan based upon a retrospective study focused on the decade 1999-2011. The results show that a major risk factor is represented by coinfections, mostly measles, and the severe malnutrition that affects children in Nigeria and sub-Saharan regions. Both risk factors cause immunosuppression that eventually leads to the onset of noma [13].

Other identified risk factors are malaria, debilitating diseases such as chickenpox, smallpox, typhoid fever, diphtheria, tuberculosis and lastly poor oral hygiene. The deriving diminution of host defenses promotes the selective growth of bacterial pathogens and alters the neutrophilic and lymphocytic function. This leads to acute necrotizing gingivitis and may potentially evolve in noma. The onset of noma deriving from necrotizing gingivitis still needs to be precisely explained [14].

Although Borrelia vincentii and Prevotella intermedia are nowadays detected as the major etiologic agents, some cases refer to the infection of unusual bacteriological species [15].

In 2018, Aastha Gupta, Kabir Sardana and Ram K Gautam reported a case of a about 3-year-old male patient with noma affecting his lower lip. After the failure of the antibiotic therapy, a bacteriological culture was conducted and showed the presence of *Klebisella pneumoniae*. The treatment was consequently substituted and brought to the healing of noma. This proves the importance of the bacteriological analysis of the necrotic ulcer in the understanding of the pathological process underlying noma and, consequently, in the selection of therapy [16].

The case of Morgagni Museum

The Morgagni Museum of Human Anatomy of the University of Padua (Italy) hosts more than 1300 pathological specimens mainly from the late 18th century to the mid-20th century, preserved either in liquid or dry [17,18,19].

Three of them, a head showing dystrophic gangrenous ulcer perforating the left cheek labelled as noma, a mesenteric lymphatic ganglion, and a spleen, belong to the same individual: a 15-year-old male individual from Padua, who died in 1902 (Fig. 1).

A detailed analysis of this case was conducted by Ettore Ravenna (1876-1963), assistant to Augusto Bonome (1857-1922), director of the Pathological Institute of the University of Padua, providing a detailed description of the specimens from a bacteriological perspective, following the teachings of Bonome [20].

Figure 1. The three specimens preserved at the Morgagni Museum: (a) patient's face with noma, (b) mesenteric lymphatic ganglion and (c) spleen.

In 1902, the patient contracted typhoid fever, a relatively common infection in that period and in that geographic area. The disease evolved with a linear pattern. The symptoms lasted 3.5 weeks, but after being apyretic for four days a necrotic lesion began to appear on his left cheek. The ulcer spread rapidly, as confirmed by the dimensions of the wound: as he entered Padua's hospital the diameter measured 2.5 cm and one week later it tripled to 8 cm. The patient died in only one week [21].

The autopsy report revealed significant general weakening and immunosuppression, leading to multiple organ failure. The cerebral tissues were infiltrated with a yellowish serous exudate indicative of purulent meningitis, likely secondary to the typhoid infection. The lungs exhibited multiple subpleural hemorrhages in the left lobe and signs of congestion in the right lobe. The kidneys were inflamed and affected by acute parenchymatous nephritis. The liver showed signs of fatty degeneration, though no bacterial species were detected in the organ. The spleen was notably enlarged, with its volume doubled, consistency reduced, and color deep red. Lastly, the mesenteric lymph nodes did not display the typical intestinal lesions associated with typhoid fever; instead, they were swollen due to lymphadenitis.

The patient's kidneys, cerebral tissues, lungs, and liver are not preserved in the collection of the Morgagni Museum.

The bacteriological analysis

Ettore Ravenna conducted an extensive bacteriological analysis of the patient's organs, with the most notable findings originating from the necrotic lesion on the left cheek, the spleen, and the mesenteric lymph nodes.

To differentiate microbial species, Ravenna employed Gram, Ziehl-Neelsen (fuchsin), and Nicolle (carbol thionin) staining techniques. To validate these results, anaerobic cultures were cultivated on agar, glycerin agar, and lactic agar mediums. The presence of plasma cells was assessed using Pappenheim staining, which incorporates methyl green and pyronin, while the detection of elastic fibers was confirmed through Taenzer-Unna staining with acid orcein and Weigert staining utilizing resorcinol and fuchsin.

The noma lesion exhibited a central necrotic area characterized by complete tissue destruction, surrounded by a peripheral zone where the necrotic process was in its early stages. There was a progressive transition from healthy tissues to the central necrotic region, with the necrosis also extending into the lower jaw (Fig. 2).

Bacteriological examinations identified the presence of the typhus bacillus, also known as the Eberth bacillus or *Salmonella enterica* serovar Typhi, predominantly within the central necrotic area and gradually permeating the adjacent healthy tissue. This was corroborated by negative Gram staining and pronounced staining with both Ziehl-fuchsin and Nicolle-carbol thionin. The typhus bacilli demonstrated slow growth in anaerobic cultures on agar, glycerin agar, and lactic agar, exhibiting a morphology that was shorter and thicker in glycerin agar and longer and thinner in standard agar.

Additionally, *Staphylococcus aureus* was isolated, primarily from the peripheral region of the lesion. These bacteria displayed Gram-positive staining and exhibited the characteristic golden appearance under microscopic examination.

Pappenheim staining yielded negative results for plasma cells in both the central necrotic and peripheral

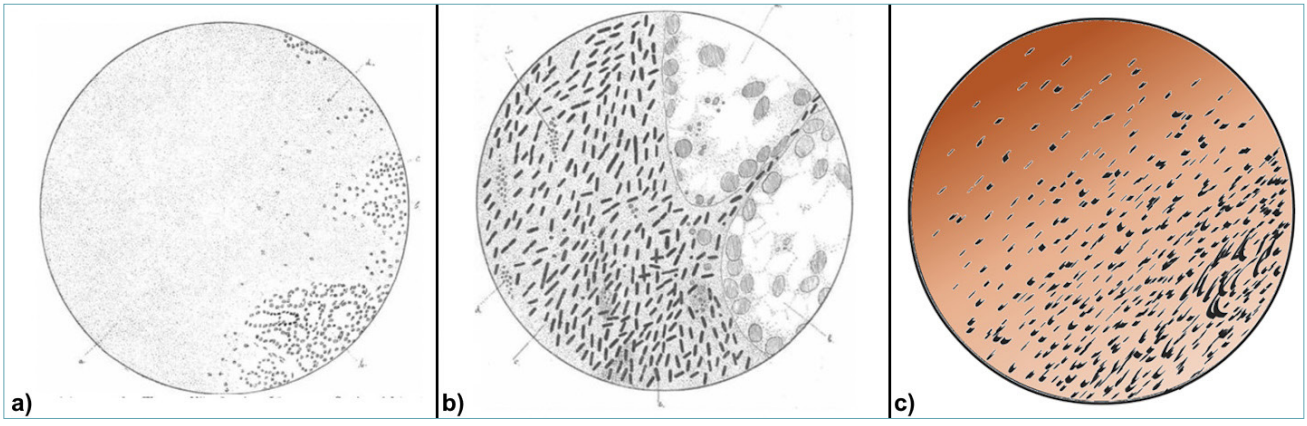

Figure 2. (a), (b) Original figures by Curt Schimmelbusch showing sharp contrast between necrotic area and healthy tissues in the noma lesion, compared with (c) progressive transition from healthy tissues to the central necrotic region as described by Ettore Ravenna (original figure by Irene Kollhof)

areas of the ulcer. However, Weigert and Taenzer-Unna staining for elastic fibers showed positive results at the interface between the two regions, confirming the presence of connective tissue within the lesion.

The analysis confirmed a gradual progression of the noma, in contrast to the findings reported by other authors [8]. No significant bacteriological differences were observed between the necrotic area and the peripheral region.

Ettore Ravenna hypothesized that the distinct histological progression observed was attributable to the characteristics of the bacteriological species involved. The Eberth bacillus, known for its strong mobility, typically multiplies within necrotic areas and gradually spreads into healthy tissues. This behavior explains why the typhus bacillus caused parvocellular infiltration, resulting in an indistinct boundary between necrotic and unaffected regions.

Microbiological analysis of the spleen confirmed the presence of abundant typhus bacilli. Additionally, Gram and Ziehl-Neelsen staining identified small clusters of cocci, consistent with *Staphylococcus aureus*.

Further examination of the lymph nodes revealed lower concentrations of typhus bacilli, with the mesenteric lymphatic ganglia identified as the primary site of initial typhus proliferation.

Through detailed micro-bacteriological analysis, Ravenna was able to propose a pathophysiological mechanism underlying the development of noma on the left cheek of the typhoid patient. The mesenteric lymphatic ganglia, spleen, and liver were identified as the first organs affected by the typhoid infection. It is likely that the typhus bacilli persisted in the bile, leading to renewed proliferation in the digestive tract and causing secondary septicemia. This progression ultimately resulted in the onset of meningitis and the development of noma on the left cheek [21].

A brief summary of the results obtained by Ravenna is presented in Table I.

Table I. Summary of the results of the bacteriological analysis.

	Central necrotic area	Peripheral area
Typhus bacilli (Nicolle staining)	Strongly positive	Parvicellular infiltration
Staphylococcus aureus (Gram staining)	Positive, with gradual increase in the number	Weakly positive
Plasma cells (Pappenheim staining)	Negative	Positive
Elastic fibers (Weigert staining)	Positive in the border zone	Positive

Discussion

As noted in earlier studies, numerous cases of noma have been associated with typhoid infections, although the precise pathogenetic mechanisms underlying the co-evolution of these two diseases remain unconfirmed. Ettore Ravenna's findings align with the analyses of both his predecessors and successors, supporting the view that noma is a consequence of immunosuppression due to concurrent infections.

Ravenna's microbiological analysis revealed the presence of both *Staphylococcus aureus* and typhus bacilli in the necrotic lesion on the child's cheek. Similar etiological pathogens had been identified in cases of noma in previous studies dating back to the 19th century [3,7,8,9,11,12].

Furthermore, Ravenna's findings are consistent with later case studies. A comparison of the bacteriological species described in recent reviews of noma cases reveals certain similarities. For instance, *Fusobacterium necrophorum* and *Prevotella intermedia* – the most detected bacteria in these cases – are both Gram-negative, obligate anaerobes, akin to the typhus bacilli identified by Ravenna. This suggests that noma is primarily caused by Gram-negative bacteria that thrive under anaerobic conditions. However, Ravenna's findings introduce a notable exception: the presence of *Staphylococcus aureus*, a Gram-positive, facultative anaerobe [21].

Further research may elucidate whether noma results from a combination of anaerobic and aerobic species, or if the necrosis is solely induced by anaerobic bacteria. Ravenna was among the first to hypothesize that the etiological agents of noma are likely not specific to a single pathogen but result from a bacteriological symbiosis.

Ettore Ravenna's analysis of the 15-year-old patient holds particular significance in advancing the understanding of noma. Unlike other authors, Ravenna preserved the specimens from the case and provided a thorough autoptic review, allowing for the possibility of re-examining the findings. This is especially valuable given that noma remains poorly studied today, with medical interest primarily focused on its treatment rather than its pathogenetic evolution.

A more in-depth investigation into the bacteriological species colonizing the necrotic lesions of noma could lead to a more precise identification of therapeutic targets and the development of more effective antibiotics. As demonstrated in other reported cases, appropriate antibiotic therapy greatly improves the chances of resolving the infectious process, healing necrotic lesions, and reducing the long-term consequences of noma [16].

Such advancements could also enhance the specificity and effectiveness of prevention campaigns, potentially reducing the severe sequelae associated with noma. Moreover, progress in bacteriological analysis of noma cases could deepen our understanding of the microbiological interactions between bacteria. Insights into the symbiotic phenomena underlying these interactions could have broader implications, leading to significant advances in the treatment of other infectious diseases, particularly those affecting immunocompromised patients.

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Conflicts of interest statement

All authors have no conflict of interest to report.

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Authors' contributions

IK: Conceptualization; Methodology; Formal analysis and investigation; Writing - original draft preparation; Writing - review and editing. GM: Conceptualization; Methodology; Formal analysis and investigation; Writing - review and editing: Supervision.

Ethical consideration

Not applicable.

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