Annals of Clinical Case Reports

Case Report
Published: 25 Feb, 2025

The Use of ChatGPT in Diagnosing Tularemia– A Case Report on the Associated Challenges and Treatment

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Abstract

The increasing use of Artificial Intelligence (AI) requires heightened sensitivity, especially in medical applications. We report a case of tularemia with a prolonged disease course, where the diagnosis was made through the pioneering use of AI by the patient himself. In this context, the use, opportunities, and risks of AI in medicine are examined in the context of rare diseases. Furthermore, the challenges of diagnosing and treating tularemia are discussed, especially as rising incidences are lately being reported in Germany.

Keywords: Tularemia, Francisella tularensis, AI, ChatGPT, Rare diseases

Introduction

In 2024, the basic research for artificial intelligence (AI) was awarded the Nobel Prize in Physics. This technology is no longer just a part of modern medicine but has also become widely accessible – a case report on an unusual synergy with emerging potential for diagnosis and treatment.

Case Presentation

A 55-year-old patient with no relevant medical history presented to his general practitioner (day 6) with increasing headaches, muscle pain, fever, night sweats, and right-sided inguinal pain for a week. His travel and sexual history were unremarkable. Professionally, he has recently been working as an artist, drawing outdoors. Due to the severity of his symptoms, he was admitted to a hospital. On examination, along with sonographically enlarged right inguinal lymph nodes an erythematous erosion was observed on the medial right calf, which initially was interpreted as an insect bite (Figure 1). The differential diagnosis was leaning toward a febrile viral infection and an inflamed injection site. An intravenous antibiotic treatment with Ampicillin/Sulbactam was initiated. He was discharged after 5 days with persistent ailments and switched antibiotic treatment to an oral form (Amoxicillin) for a total of 12 days, with worsening symptoms, the patient was prescribed Azithromycin for five days by his general practitioner (day 22). Despite this, the lymph node swelling with increasing pain intensity became more dynamic (Figure 2), leading to another admission to a hospital (day 27). The patient was diagnosed with acute lymphadenitis without need for immediate surgical intervention. Further tests for Human Immunodeficiency Virus (HIV), *Borrelia*, *Chlamydia* and *Gonococcus* were negative. Finally, the patient presented to the surgical clinic of the Bundeswehrkrankenhaus in Berlin (day 35). In consultation with the Department of Internal Medicine, a lymph node excision was postponed due to suspected infectious disease, and a calculated antibiotic regimen with Doxycycline 100 mg twice a day was initiated. Further serological diagnostics particularly for lymphotropic pathogens such as *Treponema pallidum, Toxoplasma gondii* or *Coxiella burnetii were negative*. Due to the prolonged and unclear course of illness, the patient eventually began to conduct research independently using an AI-supported online search.

AI in Medicine and Society

AI primarily originates from the imitation of human way of thinking through data recognition.

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Received Date: *13 Feb 2025*
Accepted Date*: 24 Feb 2025*
Published Date*: 25 Feb 2025*

Citation:
Kim J, Müller N, Wagelöhner T, Köppen D, Jacob D, Heuner K, et al. The Use of ChatGPT in Diagnosing Tularemia– A Case Report on the Associated Challenges and Treatment. Ann Clin Case Rep. 2025; 10: 2729.
ISSN: 2474-1655.

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Its increasing complexity arises from "advanced" forms such as "machine learning," and further from developments like multi-layered neural networks, such as "deep learning," which involve both self-learning and multi-layered analysis. In this way, AI can imitate human abilities like learning from experience, problem-solving, and decision-making without explicit programming [1]. Artificial Intelligence now touches most areas of medicine, from the production of medical goods to diagnostics, treatment, and research in all its facets. Its application holds great potential for rationalization in all areas of applied medicine and in the structural components of the entire healthcare system [2]. The most well-known AI system is probably ChatGPT (Chat Generative Pre-Training Transformer) from OpenAI, which is capable of both summarizing and answering complex topics and naturally reproducing human language through large text data and deep learning. This application is used as a dialogue system (large language model) and is accessible to everyone via the internet. Using ChatGPT, the patient extensively explored his long medical history. In pursuing this, tularemia was mentioned alongside *lyme disease*, *lymphogranuloma venereum*, *west nile virus*, *dengue fever*, and *Arboviruses*. The patient then reached out to the consultant laboratory (KL) for *Francisella tularensis* at the Robert Koch Institute (RKI) and delivered samples directly (day 34). The findings confirmed the diagnosis of tularemia.

Methods

The patient's daily medical diary allowed for a traceable course of his illness since its onset. The AI-supported dialogue was also available. For the case discussion, both case-specific and AI-related literature were researched online using PubMed. The patient has given written consent for the publication of the case, including the findings and images.

Diagnostic of tularemia

1. Indirect Pathogen Detection via Enzyme-Linked Immunosorbent Assay (ELISA): On day 34 and day 41, serum samples (A-2610, A-2627) from the patient were analyzed at the KL. The ELISA used is an in-house method designed to detect specific antibodies against the lipopolysaccharide (LPS) of *F. tularensis*, accredited according to DIN EN ISO 15189:2024, and previously described by Jenzora et al. [3]. In summary, a 96-well microtiter plate (Nunc-Polysorb, ThermoFisher Scientific, Berlin, Germany) was coated with purified LPS from the live vaccine strain of *F. tularensis* (Micromun, Greifswald, Germany). 100 µl volume of the serum diluted 1:500 (or further serial dilutions) was added to the microtiter plate. Using polyvalent or monovalent goat anti-human IgA, IgM, and IgG horseradish peroxidase-conjugated secondary antibodies (Dianova, Hamburg, Germany) and subsequent substrate reaction, bound human antibodies against *F. tularensis* LPS were detected. Serum dilutions starting from 1:500, which resulted in an optical density above the validated cut-off, were considered positive. For both serum samples (A-2610, A-2627), antibodies against the lipopolysaccharide of *F. tularensis* were detected with IgG titers of approximately 1:8000 and IgM titers of approximately 1:32,000.

2. Direct Pathogen Detection via real-time PCR and subspecies differentiation with RD1-PCR: Tissue from two different regions of the surgically removed lymph node (A-2646/1-2, sample received on November 1, 2014) was examined at the KL. Genomic DNA was first extracted from the lymph node tissue using the QIAGEN DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions [4]. The DNA elution was performed in 100 µL QIAGEN Elution Buffer (Qiagen). 5 µl aliquot of the eluted DNA was used for multiplex real-time PCR (5′-nuclease assay, TaqMan technology) targeting fopA and tul4, which are specific to *F. tularensis*, in combination with the extraction and amplification control for KoMa2, in a total volume of 25 µL, run in duplicate [4]. The c-myc gene was used as an internal extraction control and was processed as a singleplex real-time PCR assay for human specimen samples. The amplification was performed using an Applied Biosystems 7500 Real-Time PCR System (ThermoFisher Scientific, Langenselbold, Germany), with each run consisting of 40 cycles. The RD1-PCR (Region of Difference 1) was used to differentiate the subspecies of *F. tularensis*. PCR was performed with 15-100 ng of template DNA according to the protocol described by Broekhuijsen et al. [5]. The Ct values (threshold-cycle) for the real-time PCR targeting fopA and tul4 were 32 to 34. The RD1-PCR showed a band at 924 bp, confirming the presence of *F. tularensis* subspecies *holarctica* by molecular genetic methods.

3. Cultivation on Selective and Non-selective Media: Additionally, the lymph node tissue (A-2646/1-2, sample received on November 1, 2014) was cultured on MTKH agar plates (medium T supplemented with 2.4 g/l activated charcoal, 9.5 g/l hemoglobin, and 14.3 g/l agar), commercial Neisseria selective medium Plus, and chocolate agar plates (both Oxoid, Wesel, Germany) at 37°C and 5% CO2 for up to 7 days. For differential diagnoses, the samples were also plated on commercial Columbia blood agar plates (Oxoid). For enrichment, the liquid medium T, as described by Becker et al. [6], was used. No growth of the pathogen was observed, so an antibiotic susceptibility test was not conducted.

Rare infectious diseases

Despite varying terminology, rare diseases typically exhibit prevalences of less than 40-50 per 100,000 inhabitants [7]. These diseases are marked by a prolonged diagnostic process, which commonly leads to repeated hospital stays as symptoms either persist or worsen. This can result in increased mortality and morbidity. Therefore, a proper approach to such diseases requires both the reporting and documentation of cases, as well as interdisciplinary collaboration to manage them effectively.

Tularemia is a zoonosis primarily found in the Northern Hemisphere, characterized by high virulence. The bacterium *F. tularensis* was first described in Tulare County, California, in 1912, which is an aerobic gram-negative and facultatively intracellular pathogen [8,9]. It is transmitted through direct contact with infected animals, vectors like mosquitoes or ticks, aerosols, or contaminated food and water. Human-to-human transmission has not been described yet [10]. Evasion mechanisms of the innate immune system, such as the presence of poorly immunogenic components like LPS and the manipulation of host cellular metabolism to favor bacterial replication, are features contributing to the high virulence and pathogenicity of *F. tularensis* [11]. Depending on the form of the disease and subspecies, distinct manifestations may appear, with the ulceroglandular form (42-75%) and the glandular form (15-44%) being the most common. Globally, the fatality rate for Type B infections caused by *F. tularensis* subspecies *holarctica* is less than 1%, while for Type A infections caused by *F. tularensis* subspecies *tularensis*, the fatality rate is 2-3%. Severe cases, especially untreated pulmonary or typhoidal forms, can have a fatality rate of up to 30%. Systemic complications, such as meningitis, endocarditis, or prosthetic infections, are also

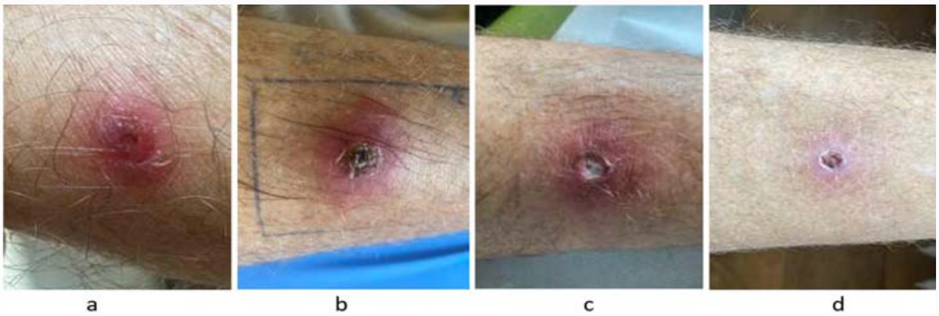

Figure 1: Course of the insect bite on the right medial calf.
a. clinical finding on day 6 **b.** day 10 **c.** day 15 **d.** day 33.

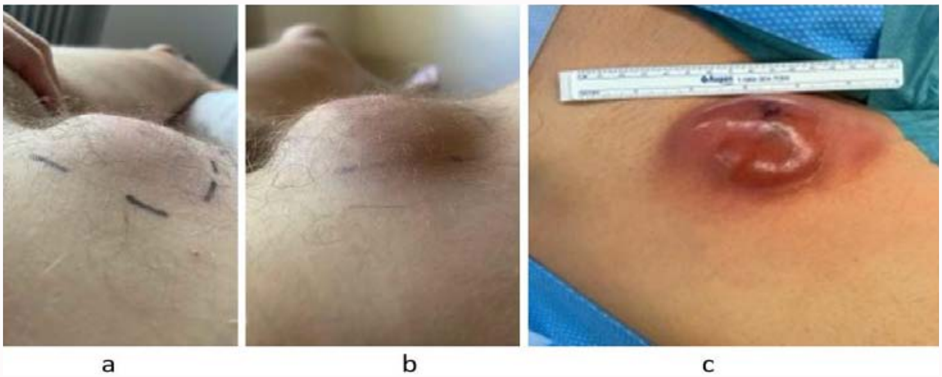

Figure 2: Progress of the right inguinal lymphadenitis.
a. clinical finding on day 30 **b.** day 35 **c.** pre-operative imaging on day 52.

Figure 3: Pre-operative CT scan of the right inguinal lymph node.

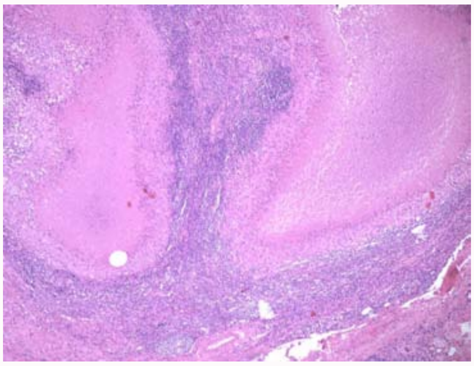

Figure 4: Histopathology of the extirpated lymph node in hematoxylin and eosin stain, granuloma with necrosis, 4x magnification

possible [12]. In 2019, the European Centre for Disease Prevention and Control reported an incidence of 0.3 cases per 100,000 inhabitants in the European Union. Since 2016, the number of reported human cases has been on the rise in Germany, ... [13].

Besides, there is potential of using tularemia as a biological weapon. The military relevance therefore appears to be even more important, especially as soldiers must be considered a risk group due to general risk of infection [14].

Therapy and Course

In cases of mild or moderate disease, ambulatory treatment with ciprofloxacin 500 mg twice daily for 10-14 days or doxycycline 100 mg twice daily for 14-21 days is recommended in Germany [15]. For severe cases requiring hospitalization, a combination with gentamicin (intravenous, 5 mg/kg once daily) and ciprofloxacin (500 mg orally or 400 mg intravenously twice daily) for 10-14 days is advised. Beta-lactams, macrolide antibiotics, and lincosamides are ineffective [15]. A combination of rifampicin and ciprofloxacin has shown to be an effective alternative *in vitro* [15,16].

In the case of the patient, a typical course of the ulceroglandular form was observed. Following this, the patient was admitted to the hospital on day 35, as there was only a moderate response to doxycycline, and an escalated antibiotic treatment with ciprofloxacin (500 mg twice daily) and gentamicin (10mg/kg for 3 days) was initiated. Although the patient's general condition improved under the initiated antibiotic treatment, the inguinal symptoms persisted. After 14 days of blood culture incubation, no microbial growth was detected. In the further course, CT imaging (Figure 3) showed increased necrosis with signs of abscess formation in the lymph node, leading to a surgical excision (day 52). In addition, due to the persistent lymphadenitis, the antibiotic treatment was continued with ciprofloxacin (500 mg twice daily) in combination with rifampicin (600 mg once daily) for another two weeks. The lymph node specimen revealed characteristic histopathological features of tularemia (Figure 4): Numerous well-formed granulomas are scattered throughout the tissue, each delineated by a collar of epithelioid macrophages and occasional Langhans-type multinucleated giant cells. Within these granulomas, central areas exhibit caseating necrosis, appearing as amorphous, eosinophilic regions with a loss of cellular architecture. Microbiologically, no pathogens were detected in the sampled tissue or pus. A PCR test conducted at the KL confirmed the presence of *F. tularensis* subspecies *holarctica*, while no pathogen growth occurred, and thus, no antibiogram was possible. Further diagnostics for Mycobacterium tuberculosis were negative.

Discussion

In the presented case, an initial targeted antibiotic treatment with ciprofloxacin and gentamicin (administered for 3 days) was used over the course of 14 days to address the patient's protracted clinical course due to the delayed diagnosis. In terms of lymph node involvement, no significant improvement was achieved. Currently, therapies for tularemia vary in their duration and composition based on disease course, complications, and patient age, and thus no uniform recommendation exists [12]. Success rates are typically observed when antibiotic treatment is initiated directly after diagnosis, preferably within 2-3 weeks of symptom onset. Delayed treatment, particularly when initiated more than 3 weeks after symptom onset, is often associated with treatment failure, recurrences, and complications, frequently requiring surgical intervention [12]. This case emphasizes the possibility of improving outcomes with prolonged and dual antibiotic treatment beyond the currently recommended duration in Germany, especially in severe cases where treatment is initiated with delay. Such an approach could potentially improve therapeutic outcomes and prevent the need for surgery [12,16,17]. Furthermore, this case illustrates a typical course of a rare disease, with an extended diagnostic process and empirical treatment that was accompanied by a progressive disease course and frequent medical consultation. A pivotal moment in the diagnostic process was marked by the patient's use of ChatGPT. This case, therefore, exemplifies the limitations of the traditional medical approach in diagnosing rare diseases, but it also highlights the potential AI brings to the medical field. It became apparent that many clinicians possess limited knowledge of rare diseases, and they are often constrained by time limitations, preventing them from effectively managing such complex cases [18-20]. These factors contribute to a significant gap in healthcare that could be addressed through the use of AI, such as ChatGPT. AI technologies hold significant potential in improving diagnostics, treatment, and prognosis of these diseases [21]. ChatGPT can serve as a supportive tool in medical research and diagnostics, potentially saving time and increasing productivity for medical professionals [22]. Two specific uses of ChatGPT in the case can be identified: 1. Supportive role in the clinical decision-making process. 2. Inquiry for medical knowledge, such as rare disease information. In studies evaluating ChatGPT's role in clinical decision-making, its performance was assessed against clinical literature. They suggest that ChatGPT can indeed assist in clinical decision-making but with limitations, especially in terms of up-to-date knowledge and the patient-specific context, as it generates responses from fixed training data [23]. Despite its broad medical knowledge, particularly on rare diseases, ChatGPT's performance still exhibits notable inaccuracies, especially in specialized areas. This highlights the need for continuous development and professional oversight to ensure its safe and effective use in medical contexts [23]. One of the key concerns in using AI in medicine is its potential ethical and data privacy implications, as well as its reliance on non-transparent datasets that may introduce biases into clinical practice [22,23].

Additionally, AI demonstrates notable advantages in certain areas, such as empathy and communication quality, where it is able to outperform human clinicians [24,25]. The results suggest that, with the increasing pace of modern medicine, medical quality and the human conscience may gradually recede into the background. The same pattern was observed in the patient dialogue with ChatGPT in this case. However, the future potential of AI is emerging, indicating that sensitivity to not only rare diseases but also modern technologies must be enhanced and leveraged to advantage. In conclusion, AI tools such as ChatGPT can assist clinicians with diagnosis, treatment planning and patient care. A strategic integration into the healthcare system, ensuring that human oversight and professional judgment remain central, should be considered, especially for rare and complex conditions.

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