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CASE REPORT

Using Targeted Next-Generation Sequencing to Diagnose Severe Pneumonia Due to Tropheryma Whipplei and Human Metapneumovirus: A Case Report and Literature Review

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Background: In addition to the well-known Whipple's disease (WD), Tropheryma Whipplei (TW) can also lead to acute pneumonia. There is no unified consensus on the susceptible population, pathogenesis, clinical manifestations, diagnostic criteria, and treatment options for TW pneumonia.

Clinical Presentation and Intervention: This is an elderly patient with multiple injuries caused by falling from a building, and was transferred to intensive care unit (ICU) for mechanical ventilation and empirical anti-infection treatment due to severe pneumonia, and then the results of targeted next-generation sequencing (tNGS) in patient's bronchoalveolar lavage fluid (BALF) suggested TW and human metapneumovirus (HMPV) infection, and after switching to anti-infective therapy for TW, the patient was successfully extubated and transferred out of the ICU.

Conclusion: This is the first case of using tNGS to diagnose severe pneumonia caused by TW and HMPV. We hope that our study can serve as a reference for the diagnosis and treatment of related cases in the future.

Keywords: Tropheryma Whipplei, bronchoalveolar lavage fluid, targeted next-generation sequencing, human metapneumovirus

Back Ground

Whipple's disease was originally named by George Hoyt Whipple in 1907.[1] It is a rare chronic systemic disease caused by Tropheryma Whipple, mainly manifested by joint pain, chronic diarrhea, and weight loss,[2] and its prevalence is about 1 in 1 million.[3] After exposure to TW, most of the body will produce asymptomatic seroconversion, and a few will cause acute TW infection, mainly manifested by acute gastroenteritis, pneumonia, and bacteremia.[4] As only limited data exist on these clinical manifestations, further research is required to determine the exact involvement of the bacterium in these acute infections.[2] J. Kirk Harris et al[5] first detected the sequence of TW in BALF in pediatric patients with acute interstitial lung disease; this suggests that TW may be a pathogen of the respiratory tract. Subsequently, Sabri Bousbia et al[6] tested BALF from ICU pneumonia patients in France by 16S rDNA and quantitative polymerase chain reaction (qPCR), and found that among the 210 BALF specimens, TW DNA was detected in 6 samples, and only TW DNA was detected in 1 sample, which highly suggests that TW can cause pneumonia. In 2011, TW was cultured for the first time as the sole causative agent from bronchoalveolar lavage fluid of an elderly female patient presenting primarily with fever, night sweats, and respiratory distress, reinforcing its role as a respiratory pathogen.[7] In recent years, with the clinical use of mNGS, cases of TW pneumonia have occasionally been

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reported.[8–10] While, there is no unified understanding of the susceptible population, pathogenesis, clinical manifestations, diagnostic criteria, and treatment plans for TW pneumonia.

In our case report, a patient was diagnosed with severe pneumonia caused by TW and HMPV through tNGS, and with targeted treatment, the patient was successfully extubated and transferred out of the ICU. Through this case, we would like to share with you the experience of diagnosis and treatment of severe pneumonia caused by the co-infection of TW and HMPV.

Case Report

Patient Presentation

On August 19, 2023, a 60-year-old man was hospitalized in the Department of Orthopedics of Jiangxi Provincial People's Hospital because of multiple fractures in his body caused by falling from the 3rd floor. The injury resulted in lung contusions and multiple fractures, including the lumbar vertebrae, multiple ribs, and pelvis. From the second day of admission, the patient occasionally experiences low-grade fever. On August 23, the patient began to show symptoms of cough and expectoration. On August 28, the patient developed symptoms of vomiting, vomiting large amounts of stomach content, subsequently, the patient experienced dyspnea and recurrent declines in pulse oxygen saturation, reaching a nadir of 86%, and the re-examination of CT on August 29 showed that pneumonia had progressed significantly compared with before. Considering severe pneumonia, he was transferred to the ICU for invasive ventilation, prone position, imipenem combined with tigecycline for anti-infective therapy. However, the patient still has recurrent fever (moderate-high fever). The patient has no previous history of underlying medical conditions and surgery, and no history of immunosuppressant use.

Diagnosis

After the patient was admitted to the ICU, the body temperature was 39.2°C, the respiratory rate reached 27 times/min, the oxygenation index was about equal to 150 (in the case of high-flow nasal cannula oxygen therapy, the fraction of inspired oxygen was 60%), a large number of wet rales could be heard on auscultation of both lungs, the blood routine showed that the white blood cell count was 10.46×10^9/L, the percentage of neutrophils was 89.2%, IL-6 was 126.36pg/mL, the procalcitonin level was 2.47ng/mL. 1-3-β-D glucan detection, aspergillus galactomannan detection, and Covid-19 nucleic acid test and sputum culture were negative. The value of NT-proBNP is 624pg/mL. The CD4-positive cell count was 203/ul, the blood lactate level was normal. Chest CT showed multiple pneumonia in both lungs (as shown in Figure 1). The echocardiogram shows normal size of the left and right atria and ventricles, with a left ventricular ejection fraction of 57%. BALF tNGS (as shown in Figure 2) showed TW (sequence number 867) and human metapneumovirus (sequence number 127). And the tNGS target panel we used includes specific sequences of a total of 500 pathogenic microorganisms, including 244 bacteria, 97 fungi, 56 DNA viruses, 47 RNA viruses, and 56 non-specific pathogens. It also includes specific sequences of 100 drug-resistant genes.

Therapy

While hospitalized in the orthopedic ward, the patient began to have repeated fever. Subsequently, the patient gradually developed cough, sputum, shortness of breath, and repeated drops of pulse oxygen. On August 26, the patient was given cefoperazone (2.0g, Q8h) as anti-infection treatment, but the symptoms did not improve. After being transferred to the ICU on August 29, the patient was given high-flow nasal cannula (HFNC), imipenem (0.5gQ6h) as anti-infection treatment. Invasive mechanical ventilation treatment was given on August 30, and tigecycline (100mg Q12h) was added on August 31. The patient's tNGS indicated TW and HMPV infection. Because we do not know much about the bacteria, the anti-infection treatment was not changed in time, but the patient still presented with medium–high fever. On September 03, imipenem and tigecycline were stopped, and meropenem combined with co-trimoxazole (SMZ) was used to fight infection. The patient's temperature soon returned to normal, and then the tracheal intubation was removed, and he was transferred back to the general ward for further treatment on September 06.

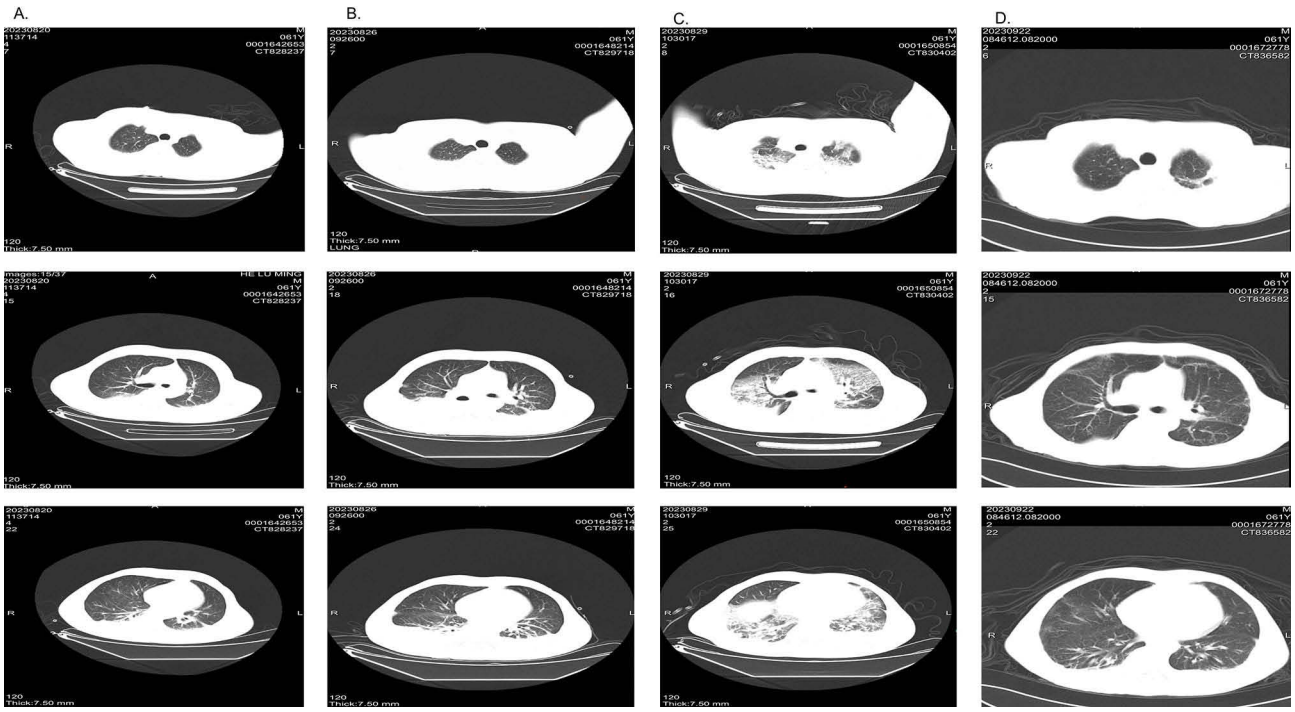

Figure 1 Chest CT Scan: (**A**) the first column, August 20th; (**B**) the second column, August 26th; (**C**) the third column, August 29th; (**D**) the fourth column, September 22nd.

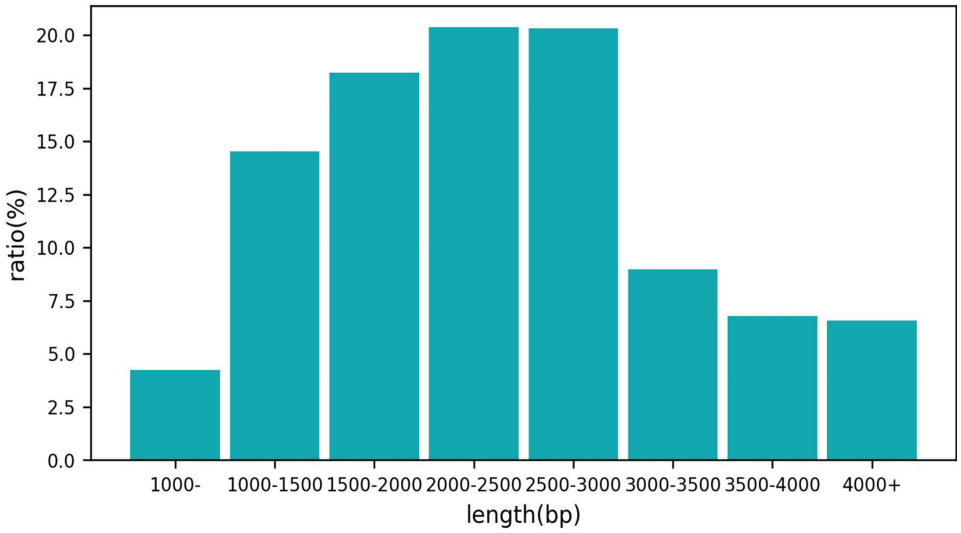

Figure 2 The patient's tNGS sequence length statistics. The sequence number of TW is 867, and the signal strength is medium. The sequence number of HMPV is 127, and the signal strength is medium. The tNGS also suggests that there are two types of background microbes, Abiotrophia defectiva, and Veillonella parvula.

Discussion

We first learned about TW mainly because of WD, a rare infectious disease.[11] There is now growing evidence that TW is associated with acute pneumonia. Even in many literature and case reports, TW is the only pathogen found in the BALF of pneumonia patients,[6,7,12,13] but the mechanism by which it causes pneumonia remains unclear. Some scholars believe that because macrophages are the main target cells of Whipple's infection, and there are a large number of macrophages in alveolar tissue, this may provide an appropriate ecological niche for TW.[2]

In this case report, considering that the progression of pneumonia occurs within the hospital, the etiology might be relatively limited, and the patient's family was not wealthy, we chose to conduct tNGS detection on the patient's BALF instead of mNGS. The patient's diagnosis was ultimately confirmed through tNGS, and the successful therapeutic effect further support the diagnose of TW pneumonia. Compared with mNGS, tNGS uses a screening process to enrich microbial sequences of interest before library preparation and sequencing,[14] it has higher sensitivity.[15] Currently, tNGS can cover more than 300 kinds of bacteria and 200 kinds of viruses.[16,17] The tNGS has been underutilized in clinical microbiology, and it may become a more accessible assay in the future[14].

TW is now recognized as a widespread bacterium, mainly transmitted between individuals through fecal–oral and oral–oral routes.[2] We cannot rule out the possibility that patients may be exposed to TW through these pathways, ultimately leading to TW pneumonia. Additionally, TW has been found in the BALF of pneumonia patients,[6,12,13] and whether it can be transmitted through the respiratory tract remains to be further studied.

TW can exist in the saliva of asymptomatic carriers,[18,19] and TW may co-cause aspiration pneumonia with other oral flora.[6] J.-C. Lagie et al[12] determined by TW PCR on 1438 BALF samples in hospitals, and the positive TW DNA of BALF was often associated with aspiration pneumonia (18/88 patients compared with 6/88 controls, p 0.01). The patient suffered from multiple fractures throughout the body due to trauma and was immobilized during hospitalization. They had weak coughing and experienced a decrease in pulse oxygen saturation after vomiting. Considering these clinical symptoms along with the presence of two common oral microbial communities in the patient's tNGS background, we still lean towards diagnosing the patient with aspiration pneumonia. Some may question whether TW and the two oral microbial communities appearing together in the tNGS report could be colonization or contamination, but we believe this possibility is unlikely. The patient exhibited typical respiratory infection symptoms, significantly elevated inflammatory markers, chest CT indicating pneumonia, and significant symptom improvement only after receiving targeted anti-infective treatment for TW. The patient's excellent treatment outcome serves as reverse evidence for the diagnosis of TW pneumonia. Unfortunately, at that time, we did not test the stool and saliva of patients for TW DNA, and it is not clear whether the patient is an asymptomatic carrier of TW.

In addition, the colonization rate of TW in the lungs of healthy patients can be as high as 26%.[20] In parallel, a higher prevalence of TW lung colonization in asymptomatic HIV-positive patients was reported compared to a control group.[21] Whether there is an association between TW colonization and TW pneumonia, if there is an association, such a high colonization rate seems to imply that we have underestimated the occurrence of TW pneumonia.

The current recommended treatment regimen for WD is either ceftriaxone (1 dose of 2 g/day) or meropenem (3 doses of 1 g/day) for 14 days, followed by oral SMZ for 12 months.[2] In vitro tests have shown that TW may be resistant to trimethoprim,[22,23] in this case, we can replace SMZ with doxycycline.[24] After referring to the antibiotic regimen for TW pneumonia reported by Wei Li et al,[9] and considering the patient's own situation, we also chose meropenem combined with SMZ. Unlike us, Sheng Wang et al[10]reported that TW pneumonia was successfully treated with imipenem. Areen Boulos et al[25] found that TW had great differences in sensitivity to imipenem in vitro, among the three strains, only Twist strains were sensitive to imipenem (MIC was 0.5 g/mL), while Endo2 and Slow strains were resistant to imipenem (MIC was 10 g/mL). I think this may be the reason why we all use imipenem, but the effect is not the same. Secondly, Kalliopi Foteinogiannopoulou et al[26] had successfully treated a WD patient who was resistant to trimethoprim by long-term intravenous use of tigecycline followed by oral doxycycline combined with hydroxychloroquine, so we also considered whether tigecycline could continue to be used as a part of treatment of TW pneumonia. Considering that the patient's tNGS did not indicate MDR-GNB infection, we did not choose tigecycline in consideration of economic and adverse drug reactions and other factors. For the special medical setting of the ICU, tigecycline may also become a new option for the treatment of TW.

In conclusion, this case report is the first reported case of severe pneumonia caused by TW and HMPV confirmed by tNGS. For the diagnosis of special pathogen infection, tNGS has higher sensitivity and economic cost saving advantages compared with mNGS, and we should also pay attention to the existence of bias by tNGS. At present, there is no uniform standard for anti-infective treatment plan and course of treatment for TW pneumonia. Piperacillin tazobactam,[8] imipenem,[10] meropenem combined with doxycycline,[8] meropenem combined with SMZ,[9] and ceftriaxone combined with SMZ[8] have all been reported to have successfully treated TW pneumonia; however, subsequent antibiotic treatment plan, TW re-infection, and TW complete elimination are not clear, and this also needs further study.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Declarations and Consent Statement

Since the data were anonymous, the need for ethics approval was waived by the Ethics Committee of the Jiangxi Provincial People's Hospital. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in-Chief of this journal.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull Johns Hopkins Hosp*. 1907;18:382–393.
2. Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. Clinical Manifestations, treatment, and diagnosis of Tropheryma whipplei infections. *Clin Microbiol Rev*. 2017;30:529–555. doi:10.1128/CMR.00033-16
3. Obst W, von Arnim U, Malfertheiner P. Whipple's Disease. *Viszeralmedizin*. 2014;30(3):167–172. PMCID: PMC4513828. doi:10.1159/000363781. PMID:26288590;
4. Puechal X. Whipple's disease. *Ann Rheum Dis*. 2013;72:797–803. doi:10.1136/annrheumdis-2012-202684
5. Harris JK, De Groote MA, Sagel SD, et al. Molecular identification of bacteria in bronchoalveolar lavage fluid from children with cystic fibrosis. *Proc Natl Acad Sci U S A*. 2007;104(51):20529–20533. PMID: 18077362; PMCID: PMC2154465. doi:10.1073/pnas.0709804104
6. Bousbia S, Papazian L, Auffray JP, et al. Tropheryma whipplei in patients with pneumonia. *Emerg Infect Dis*. 2010;16(2):25863. PMID:20113556; PMCID:PMC295799. doi:10.3201/eid1602.090610
7. Fenollar F, Ponge T, La Scola B, Lagier JC, Lefebvre M, Raoult D. First isolation of Tropheryma whipplei from bronchoalveolar fluid and clinical implications. *J Infect*. 2012;65(3):275–278. PMID: 22172770. doi:10.1016/j.jinf.2011.11.026.
8. Fang Z, Liu Q, Tang W, et al. Experience in the diagnosis and treatment of pneumonia caused by infection with Tropheryma whipplei: a case series. *Heliyon*. 2023;9(6):e17132. PMID: 37484369; PMCID: PMC10361318. doi:10.1016/j.heliyon.2023.e17132
9. Li W, Zhang Q, Xu Y, Zhang X, Huang Q, Su Z. Severe pneumonia in adults caused by Tropheryma whipplei and Candida sp. infection: a 2019 case series. *BMC Pulm Med*. 2021;21(1):29. doi:10.1186/s12890-020-01384-4
10. Wang S, Xia D, Wu J, Jia D, Li L, Xu S. Severe pneumonia caused by infection with tropheryma whipplei complicated with Acinetobacter baumannii infection: a case report involving a young woman. *Front Public Health*. 2021;9:729595. PMID: 34760862; PMCID: PMC8575073. doi:10.3389/fpubh.2021.729595
11. Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. *Lancet Infect Dis*. 2016;16(3):e13–22. PMID: 26856775. doi:10.1016/S1473-3099(15)00537-X
12. Lagier JC, Papazian L, Fenollar F, et al. Tropheryma whipplei DNA in bronchoalveolar lavage samples: a case control study. *Clin Microbiol Infect*. 2016;22(10):875–879. PMID: 27432769. doi:10.1016/j.cmi.2016.07.010
13. Stein A, Doutchi M, Fenollar F, Raoult D. Tropheryma whipplei pneumonia in a patient with HIV-2 infection. *Am J Respir Crit Care Med*. 2013;188(8):1036–1037. PMID: 24127807. doi:10.1164/rccm.201304-0692LE
14. Mitchell SL, Simner PJ. Next-generation sequencing in clinical microbiology: are we there yet? *Clin Lab Med*. 2019;39(3):405–418. PMID: 31383265. doi:10.1016/j.cll.2019.05.003

15. Williams SH, Cordey S, Bhuva N, et al. Investigation of the plasma virome from cases of unexplained febrile illness in Tanzania from 2013 to 2014: a comparative analysis between unbiased and VirCapSeq-VERT high-throughput sequencing approaches. *mSphere*. 2018;3(4):e00311–e00318. Erratum in: mSphere. 2018 Sep 19;3(5). PMID: 30135221; PMCID: PMC6106054. doi:10.1128/mSphere.00311-18
16. Briese T, Kapoor A, Mishra N, et al. Virome capture sequencing enables sensitive viral diagnosis and comprehensive virome analysis. *mBio*. 2015;6(5):e01491–e01515. Erratum in: MBio. 2017 May 16;8(3). PMID: 26396248; PMCID: PMC4611031. doi:10.1128/mBio.01491-15
17. Allicock OM, Guo C, Uhlemann AC, et al. BacCapSeq: a platform for diagnosis and characterization of bacterial infections. *mBio*. 2018;9(5):e02007–18. PMID: 30352937; PMCID: PMC6199491. doi:10.1128/mBio.02007-18
18. Fenollar F, Laouira S, Lepidi H, Rolain JM, Raoult D. Value of Tropheryma whipplei quantitative polymerase chain reaction assay for the diagnosis of Whipple disease: usefulness of saliva and stool specimens for first-line screening. *Clin Infect Dis*. 2008;47(5):659–667. PMID: 18662136. doi:10.1086/590559
19. Grasman ME, Pettersson AM, Catsburg A, Koek AG, van Bodegraven AA, Savelkoul PH. Tropheryma whipplei, a potential commensal detected in individuals undergoing routine colonoscopy. *J Clin Microbiol*. 2015;53(12):3919–3921. PMID: 26447117; PMCID: PMC4652119. doi:10.1128/JCM.02630-15
20. Morris A, Beck JM, Schloss PD, et al.; Lung HIV Microbiome Project. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. *Am J Respir Crit Care Med*. 2013;187(10):1067–1075. PMID: 23491408; PMCID: PMC3734620. doi:10.1164/rccm.201210-1913OC
21. Beck JM, Schloss PD, Venkataraman A, et al. Microbiome Project. Multicenter comparison of lung and oral microbiomes of HIV-infected and HIV-uninfected individuals. *Am J Respir Crit Care Med*. 2015;192(11):1335–1344. PMID: 26247840; PMCID: PMC4731698. doi:10.1164/rccm.201501-0128OC
22. Lagier JC, Fenollar F, Raoult D. Maladie de Whipple et infections à Tropheryma whipplei. Quand l'interniste doit y penser? Comment les traiter? [Whipple's disease and Tropheryma whipplei infections in internal medicine. When to think about it? How to treat?]. *RevMedInterne*. 2014;35(12):801–807. French. PMID: 24933290
23. Fenollar F, Perreal C, Raoult D. Tropheryma whipplei natural resistance to trimethoprim and sulphonamides in vitro. *IntJ Antimicrob Agents*. 2014;43(4):388–390. PMID: 24613421. doi:10.1016/j.ijantimicag.2014.01.015
24. Feurle GE, Moos V, Bläker H, et al. Intravenous ceftriaxone, followed by 12 or three months of oral treatment with trimethoprim-sulfamethoxazole in Whipple's disease. *J Infect*. 2013;66(3):263–270. PMID: 23291038. doi:10.1016/j.jinf.2012.12.004
25. Boulos A, Rolain JM, Raoult D. Antibiotic susceptibility of Tropheryma whipplei in MRC5 cells. *Antimicrob Agents Chemother*. 2004;48(3):747–752. PMID: 14982759; PMCID: PMC353111. doi:10.1128/AAC.48.3.747-752.2004
26. Foteinogiannopoulou K, Mouzas I, Tzardi M, Orfanoudaki E, Theodoraki E, Kofteridis D. First case of Whipple's disease successfully treated with tigecycline. *Germs*. 2021;11(1):105–110. PMID: 33898347; PMCID: PMC8057852. doi:10.18683/germs.2021.1246