

First case report- Far Eastern Scarlet Fever (FESLF) associated with Still's disease in adults.

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DOI <https://doi.org/10.64288/2a2hsx35>

Keywords: yersiniosis, *Y. pseudotuberculosis*, Still's disease, FESLF.

Abstract. *Yersiniosis is a rare and sporadic infection that is most transmitted through raw or undercooked pork products. It may present clinically with arthritis, pharyngitis, hepatitis, persistent fever, abdominal pain, mesenteric lymphadenitis, or symptoms mimicking appendicitis [1;2]. Although it is considered a sporadic infection, difficulties in culturing the organism, its high genetic similarity (64%) with closely related species (*Yersinia pestis*, *Yersinia enterocolitica*), cross-reactivity of O:9 serovars with Brucellosis, and variability in clinical presentation can lead to delays in diagnosis [3;4]. *Yersinia pseudotuberculosis* produces a superantigen called YPM (*Y. Pseudotuberculosis*-derived mitogen), which plays a key role in the pathogenesis of Far East Scarlet-Like Fever (FESLF), causing rapid proliferation of T lymphocytes and toxic shock syndrome [1]. Therefore, it tends to have a more severe clinical course compared to other forms of yersiniosis. Mortality rates range between 11% and 75% [5;6].*

*In 1984, R. Colebunders and colleagues reported a case of Still's disease associated with *Yersinia enterocolitica* [7]. There has been no previously reported clinical case linking *Yersinia pseudotuberculosis* with Still's disease. The clinical case we present demonstrates that *Yersinia pseudotuberculosis* may also be associated with Still's disease. In the presented clinical case, a diagnosis of Still's disease was established in a 19-year-old patient with confirmed *Y. pseudotuberculosis* infection, due to an inadequate therapeutic response, followed by clinical remission.*

Introduction.

Although *Yersinia pseudotuberculosis* infections occur sporadically in Europe, they have caused epidemics in Russia and Japan [8;9]. It is the only one known gram-negative bacteria that produces a superantigen, leading to a scarlet fever-like syndrome. During the 1959 epidemic of *Y. pseudotuberculosis* in the Vladivostok region of Russia, previously misdiagnosed as scarlet fever. However, later it was termed FESLF due to its distinct clinical presentation [8].

Case Report.

A 19-year-old male patient without known chronic illnesses. Clinical presented with persistent fever lasting 15 days, fatigue, joint pain, skin rashes and abdominal pain. Initially, he had two days of diarrhea. His dietary history

is related to frequent consumption of raw sausages, fast food, and energy drinks. During the illness course, he received various antibiotic regimens, including levofloxacin for 3 days, ciprofloxacin for 2 days, followed by a combination of ceftriaxone and metronidazole. On the fourth day of this last treatment, he applied to our hospital. His general condition was assessed as moderately severe. He was conscious and oriented, responding appropriately to questions. On physical examination, fever is 39.2°C, oxygen saturation (SpO₂) of 99%, and tachycardia. Macular rashes with mild pruritus were seen on the hands and feet. The oropharynx was hyperemic, abdominal palpation as well as examination of the left sacroiliac joint elicited tenderness. Laboratory investigations resulted in left-shifted leukocytosis (WBC: 19,000/μL;

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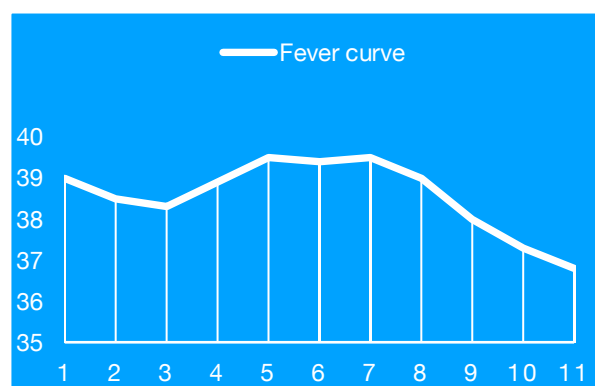
Neutrophils: 90%, IG: 2.7%), thrombocytosis (PLT: 417,000/ μ L), elevated liver enzymes (ALT: 193 U/L, AST: 137.4 U/L), coagulopathy, and elevated inflammatory markers (ESR: 29 mm/h, CRP: 90 mg/L, ferritin: >2000 ng/mL). PCT-0.4 ng/mL, ASO-312 IU/mL, while both rheumatoid factor and ANA were negative. The patient was hospitalized and empirically started on piperacillin-tazobactam. Thoracic and abdominal CT scans revealed nonspecific lymphadenopathy-involving hilar, supraclavicular, cervical, axillary, and mesenteric lymph nodes, with sizes up to 10 mm. Serologic testing for HIV, hepatitis B and C, EBV, and brucellosis was negative. Blood and urine cultures were negative.

On the fifth day of hospitalization, a sample for Yersinia testing was taken and analyzed via PCR using the Bio-Rad platform, and rheumatology consultation was performed. Patients fulfilled all Yamaguchi criteria, and although it is an exclusionary diagnosis, the diagnosis of Adult-onset Still's disease (AOSD) was made. On the same day, PCR for Yersinia enterocolitica/pseudotuberculosis was positive. Accordingly, piperacillin-tazobactam was switched to a combination of ciprofloxacin and gentamicin. The following day, a scarlatiniform rash with a Filatov triangle was observed. Despite antimicrobial therapy, fever persisted around 38°C on day three of the new regimen, prompting the initiation of methylprednisolone at 64 mg/day. With clinical stabilization and evidence of skin desquamation, patient was discharged on day six of treatment with oral trimethoprim-sulfamethoxazole (TMP-SMX).

Discussion.

The patient's frequent consumption of Russian-produced raw sausages, the initial

episode of diarrhea, and the clinical presentation led us to suspect a Yersinia



infection. Positive PCR results along with negative culture results highlighted the importance of this diagnostic approach [3]. Although the Bio-Rad device could not differentiate between Yersinia enterocolitica serovars O:3, O:9, and Yersinia pseudotuberculosis serovar T:1, the development of FELS syndrome in this patient suggested that the causative agent was the Y. pseudotuberculosis strain. This strain produces toxic superantigens, which play a significant role in the pathogenesis of FELS [8;10].

The activation of Still's disease by Y. pseudotuberculosis can be supported through several pathogenetic mechanisms. The pathogenesis of Still's disease is related to the activation of the inflammatory cascade, where PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns) trigger the activation of macrophages and neutrophils through TLRs (Toll-like receptors). The generation of these danger signals can be triggered by various bacteria and viruses, including Yersinia strains. Y. pseudotuberculosis causes hyperactivation of the immune system. Activated IL-1 β and IL-18 play crucial roles in the onset of Still's disease [11]. While previous literature has identified several viruses and intracellular bacteria (such as Chlamydia pneumoniae, Mycoplasma pneumoniae, Borrelia burgdorferi, Brucella abortus, and

Yersinia enterocolitica) in relation to the activation of Still's disease, *Y. pseudotuberculosis* had not been previously mentioned [12]. However, the genetic similarity between *Yersinia* strains further supports the relevance of this finding for *Y. pseudotuberculosis*.

There is a genetic predisposition to arthritis and the development of Still's disease in individuals with specific HLA gene alleles following a *Yersinia* infection [13;14].

Yersinia microorganisms are ferrophilic, meaning patients with disturbances in iron metabolism are at higher risk [15;16]. However, during Still's disease, the elevated ferritin levels do not result from increased iron stores but are rather an acute-phase reactant. Consequently, ferritin during this period consists of the iron-poor apoferritin form. Thus, we cannot conclude that *Yersinia* infection directly triggers Still's disease [17]. This observation is further supported by previous reports of other infections related to Still's disease.

The diagnosis of Still's disease is one of exclusion, and prior infections should be ruled out before confirming the diagnosis. However, despite five days of empirical treatment with piperacillin-tazobactam and three days of specific therapy, the patient's condition did not improve. Previous literature reports that clinical responses to *Yersinia pseudotuberculosis* infection were observed within 48 hours of piperacillin-tazobactam treatment [18]. No resistance has been reported to ciprofloxacin and gentamicin combination. Due to the persistence of the clinical presentation, Still's disease was suspected, and we initiated treatment accordingly.

Conclusion.

Although *Yersinia pseudotuberculosis* is a rare infection, it is often difficult to diagnose. The use of PCR significantly increases diagnostic

accuracy. Although not previously documented in the literature, this case demonstrates that *Y. pseudotuberculosis* can indeed trigger Still's disease. Future studies exploring the role of HLA gene polymorphisms in the pathogenesis of FELS and their correlation with clinical outcomes could provide valuable insights.

References:

1. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 229B-*Yersinia enterocolitica* and *Yersinia pseudotuberculosis* Richard R. Watkins. pages 2787-2792
2. <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-adult-onset-stills-disease>
3. Reinhardt M, Hammerl JA, Kunz K, Barac A, Nöckler K, Hertwig S. *Yersinia pseudotuberculosis* Prevalence and Diversity in Wild Boars in Northeast Germany. *Appl Environ Microbiol.* 2018 Aug 31;84(18):e00675-18. doi: 10.1128/AEM.00675-18. PMID: 29980552; PMCID: PMC6122006.
4. *Yersinia enterocolitica* «feksiyonlar» Orhan BAYLAN, H. Ercan ABASLI; *Türk Mikrobiyol Cem Derg* (2005) 35:232-247
5. Long C, Jones TF, Vugia DJ, Scheffel J, Strockbine N, Ryan P, Shiferaw B, Tauxe RV, Gould LH. *Yersinia pseudotuberculosis* and *Y. enterocolitica* infections, FoodNet, 1996-2007. *Emerg Infect Dis.* 2010 Mar;16(3):566-7. doi: 10.3201/eid1603.091106. PMID: 20202449; PMCID: PMC3322025.
6. Brady MF, Yarrarapu SNS, Anjum F. *Yersinia Pseudotuberculosis*. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430717/>
7. Colebunders R, Stevens WJ, Vanagt E, Snoeck J. Adult Still's Disease Caused by *Yersinia enterocolitica* Infection. *Arch Intern Med.* 1984;144(9):1880-1882. doi:10.1001/archinte.1984.00350210210040
8. GRUNIN II, SOMOV GP, ZALMOVER Iiu. [Far Eastern scarlatinoid fever]. *Voen Med Zh.* 1960 Aug;8:62-6. Russian. PMID: 13709268.
9. A. Amphlett, Far East Scarlet-Like Fever: A Review of the Epidemiology, Symptomatology,

- and Role of Superantigenic Toxin: *Yersinia pseudotuberculosis*-Derived Mitogen A, *Open Forum Infectious Diseases*, Volume 3, Issue 1, Winter 2016, ofv202, <https://doi.org/10.1093/ofid/ofv202>
10. Goubard ALoiez C, Abe J, Fichel C, Herwegh S, Faveeuw C, Porte R, Cayet D, Sebbane F, Penet S, Foligné B, Desreumaux P, Saito H, Sirard J, Simonet M, Carnoy C. 2015. Superantigenic *Yersinia pseudotuberculosis* Induces the Expression of Granzymes and Perforin by CD4⁺ T Cells. *Infect Immun* 83: <https://doi.org/10.1128/iai.02339-14>
 11. Feist, E., Mitrovic, S., & Fautrel, B. (2018). Mechanisms, biomarkers and targets for adult-onset Still's disease. *Nature Reviews Rheumatology*. doi:10.1038/s41584-018-0081-x
 12. Campos Nogueira A, Manuel Fernandes T, Costa Still's Disease – Unlikely Diagnosis on the Old Age. *Galicla Clin* 2019; 80 (3): 53-55 Recibido: 19/10/2018; Aceptado: 13/11/2018 // <http://doi.org/10.22546/53/1806>
 13. Shijia Rao et al., Adult-onset Still's disease: A disease at the crossroad of innate immunity and autoimmunity *Sec. Dermatology* Volume 9- 2022 | <https://doi.org/10.3389/fmed.2022.881431>
 14. Yokoyama K, Mamada M (November 10, 2024) *Yersinia pseudotuberculosis*-Associated Myositis. *Cureus* 16(11): e73399. DOI 10.7759/cureus.73399
 15. Perry RD, Fetherston JD. *Yersiniabactin* iron uptake: mechanisms and role in *Yersinia pestis* pathogenesis. *Microbes Infect.* 2011 Sep;13(10):808-17. doi: 10.1016/j.micinf.2011.04.008. Epub 2011 May 12. PMID: 21609780; PMCID: PMC3148425.
 16. Carniel E, Mazigh D, Mollaret HH. 1987. Expression of iron-regulated proteins in *Yersinia* species and their relation to virulence. *Infect Immun* 55: <https://doi.org/10.1128/iai.55.1.277-280.1987>
 17. Patel S, Monemian S, Khalid A, Dosik H. Iron Deficiency Anemia in Adult Onset Still's Disease with a Serum Ferritin of 26,387 µg/L. *Anemia*. 2011;2011:184748. doi: 10.1155/2011/184748. Epub 2011 May 12. PMID: 21738862; PMCID: PMC3124123.
 18. Zewude et al., *Yersinia pseudotuberculosis* bacteraemia with splenic abscesses: a case report *Access Microbiology* 2023;5:000525.v3 DOI 10.1099/acmi.0.000525.v3

