

## Case Report

# Fulminant Necrotizing Fasciitis and Myositis with Streptococcal Toxic Shock Syndrome in A Patient with Rheumatoid Arthritis on Tocilizumab: A Case Report

Oana Antal<sup>1,2\*</sup>, Nicolae Cezar Gorcea<sup>3</sup>, Cristina Lenuț<sup>3</sup>, Vasile Bințișan<sup>1,2</sup>, Liliana Rogoian<sup>1</sup> and Laura Damian<sup>1</sup>

<sup>1</sup>Emergency Clinical County Hospital, No 3-5 Clinicilor Street, Cluj-Napoca, 400005, Cluj, Romania

<sup>2</sup>University of Medicine and Pharmacy, Iuliu Hațieganu, No 8 Victor Babeș Street, Cluj-Napoca, 400012, Cluj, Romania

<sup>3</sup>Emergency County Hospital, No 23 Bulevardul Revoluției 1989, Alba Iulia, 510007, Alba, Romania

### Abstract

**Introduction:** We present the case of a 44-year man with a fulminant necrotizing myositis and fasciitis and streptococcal toxic shock syndrome, the patient being under treatment with tocilizumab and methotrexate for rheumatoid arthritis.

**Case presentation:** He presented to the emergency department with diarrhea, flu-like symptoms and intense progressive pain in the right thigh after having shoveled while doing building work at home. His condition deteriorated within hours, he developed severe rhabdomyolysis, multiple organ dysfunction syndrome, disseminated intravascular coagulopathy and died, despite early treatment.

**Discussion:** A great index of suspicion for severe necrotizing soft tissue infections is necessary in patients on tocilizumab or other biologic immunosuppressive agents. The possible mechanisms in this setting include lowering CRP involved in innate immune

**\*Corresponding author:** Oana Antal, Department of Anaesthesia and Intensive Care, University of Medicine and Pharmacy, Iuliu Hațieganu, Cluj-Napoca, Cluj, ROMANIA; Department of Anaesthesia and Intensive Care, Emergency Clinical County Hospital, Cluj-Napoca, Cluj, Romania, Tel: 0040744499883; E-mail: antal.oanna@gmail.com

**Citation:** Antal O, Gorcea NC, Lenuț C, Bințișan V, Rogoian L, et al. (2020) Fulminant Necrotizing Fasciitis and Myositis with Streptococcal Toxic Shock Syndrome in A Patient with Rheumatoid Arthritis on Tocilizumab. A Case Report. J Emerg Med Trauma Surg Care 7: 052.

**Received:** August 21, 2020; **Accepted:** September 22, 2020; **Published:** September 28, 2020

**Copyright:** © 2020 Antal O, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

responses, decrement of neutrophil count and function, increasing iron availability for infection, as well as high expression of vimentin, the streptococcal binding protein, by regenerating muscle fibers after trauma. Diarrhea due to endotoxins and flu-like symptoms may be early and sometimes they may be the only presenting signs of severe group A streptococcal infection in patients with blunt trauma on biologics. Low initial CRP and white blood cell count may be misleading. A rapid streptococcal strip test may help anticipate and possibly prevent a deleterious evolution in such patients.

**Conclusion:** Biologics may modify the clinical presentation of NF, the LRINEC score, and the pathology decision algorithm. A great index of suspicion for severe soft tissue infections is required in patients on biologics with blunt trauma, especially when presenting with flu-like symptoms, diarrhea, or vomiting.

**Keywords:** Case report; Group A Streptococcus; Necrotizing fasciitis; Streptococcal toxic shock syndrome; Tocilizumab

### Abbreviations

CRP: C -Reactive Protein;

GAS: Group A Streptococcal Infections;

IL-6: Interleukin-6;

LRINEC: Laboratory Risk Indicator of Necrotizing Fasciitis Score;

NF: Necrotizing Fasciitis;

RA: Rheumatoid Arthritis;

STSS: Streptococcal Shock Syndrome

### Introduction

Group A streptococcus rarely produces life-threatening, rapidly progressive invasive infections such as necrotizing fasciitis (NF) or necrotizing myositis. Tocilizumab, a humanized anti-IL-6 receptor antibody, is a very efficient biologic therapy for Rheumatoid Arthritis (RA), systemic juvenile arthritis, giant cell arteritis and others. Tocilizumab alleviates systemic signs of inflammation, such as fever, anemia and leukocytosis and decreases the C- reactive protein (CRP) [1].

Theory: Patients on immunosuppressive drugs, including tocilizumab and other biologics, may present in the Emergency Department with atypical clinical and laboratory signs of severe soft tissue infections.

### Case Description

A 44-year male patient presented with flu-like symptoms, diarrhea and intense progressive pain in the right thigh after having shoveled while doing building work at home. He had been diagnosed 3 years before with seropositive RA and had been taking ever since Methotrexate 20 mg/week and for the last 8 months tocilizumab 162 mg/week (after failing leflunomide and golimumab). In the territorial hospital, examination revealed a discretely increased in volume right thigh, with no skin laceration. Analyses showed mild inflammation (CRP 12.9 mg/L, normal 0-5 mg/L), increased CK (1269IU/L, normal

24-195 IU/L) and leukopenia (2500 WBC/ $\mu$ L). Stool cultures (and examination for parasites) were negative. Ultrasonography found only muscle edema. Clindamycin, analgesics and ice packs were given. Within a few hours the thigh pain became excruciating and his status deteriorated, with perioral and peripheral cyanosis, arterial hypotension and discoloration of the thigh; rhabdomyolysis enzymes were markedly increased at this time (CK 22170 UI/L, AST 1096 UI/L, ALT 396 UI/L). For the suspicion of NF the LRINEC score at admission time was 0, shortly reaching 6. He received large spectrum antibiotics (Meropenem, Vancomycin, Clindamycin) and underwent excision of right medial vastus and extensive fasciotomy of the right thigh. Pus was not seen. Extemporaneous histology showed diffuse, extensive, early rhabdomyolysis. He shortly developed hemorrhagic shock (Hb 5.8 g/dL), disseminated intravascular coagulation, multiple organ dysfunction (acute cardio-circulatory, renal, hematologic, respiratory and hepatic failure, neurologic dysfunction) and was transferred by helicopter to our Intensive Care Department. CVVHDF, coagulation factors (VIIa, prothrombinic complex), fibrinogen, antifibrinolytic agents, blood products (MER, PPC, cryoprecipitate, CTS), antibiotics (including Penicilline, Clindamycin, Meropenem) were given, then hemostatic surgery, extensive debridement and amputation were performed, with no effect. He presented asystole; resuscitation was ineffective. All cultures harvested from the plague and blood were positive for beta-hemolytic group *Streptococcus pyogenes*. The final histopathological findings were characteristic for both necrotizing fasciitis and myositis.

## Discussion

Necrotizing soft tissue infections include NF and necrotizing myositis, dreaded infections which may evolve within hours to fatal complications [2,3]. In NF soft tissue pain is often disproportionately intense, and other clinical findings may be scarce or late [3]. Examinations (MRI, CT, ultrasound) may help the diagnosis. An over 3 mm hyperintense fascial signal on fat-suppressed T2 MRI scan suggests NF [4]. The LRINEC (Laboratory Risk Indicator of Necrotizing Fasciitis) score was developed to early assess NF risk [5]. Early exploratory biopsy is advised, and a clinical decision algorithm was suggested based upon histopathology [2].

Importantly, group A streptococcal infections (GAS) do not produce tissue gas, while purulent discharge may be minimal [3]. Mortality of GAS- necrotizing fasciitis is 20%, but may reach even beyond 70% when complicated by streptococcal shock syndrome (STSS) [6]. Clinical presentation of STSS include, 24-48 hours before onset, high fever, chills, myalgia and often vomiting or diarrhea with negative stool cultures, as in our patient, due to streptococcal enterotoxins [3]. The source is often an upper respiratory tract infection.

*Streptococcus enter* toxins function as super antigens, able to activate large number of lymphocytes. Other factors depending on the germ and host, including RA, immunosuppression, NSAIDs or proton pump inhibitors, augment infections risk [3,7]. Blunt trauma and muscle strains, like in our case, increase NF risk with up to 85% lethality [6,7]. Vimentin expressed by regenerating muscle cells after injury is also the major skeletal muscle GAS-binding protein [7,8].

Severe soft tissue infections including NF were reported on biologics, more frequent on tocilizumab [9-14]. The pro-inflammatory cytokine IL-6 controls the liver synthesis of CRP involved in opsonization, phagocytosis and complement activation [15].

Tocilizumab decreases neutrophil count and functions, inhibits ferritin and the iron-sequestering hormone hepcidin responsible for inflammatory anemia, but makes serum iron available for bacterial growth [1,16,17].

Antibiotic therapy (penicillin and clindamycin for the antitoxin effect), surgical debridement and general support (and possibly intravenous immunoglobulin's or hyperbaric oxygen) should be instituted early [3]. Active observation and rapid antigen detection test for *Streptococcus* may shorten the time to surgery [18].

## Conclusion

Biologics may modify the clinical presentation of NF, the LRINEC score, and the pathology decision algorithm. A great index of suspicion for severe soft tissue infections is required in patients on biologics with blunt trauma, especially when presenting with flu-like symptoms, diarrhea or vomiting. Increased awareness and an informative card for emergency use could help improve the outcome.

## Conflicting Interests

The Authors declare that there is no conflict of interest.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for profit sectors.

## Informed Consent

Written informed consent was obtained from a legally authorized representative for anonymized patient.

## Ethical Approval

"Emergency Clinical County Hospital" does not require ethical approval for reporting individual cases or case series.

## Authors Contribution

Conceptualization: Laura Damian, Oana Antal. Methodology: Laura Damian, Oana Antal. Writing- original draft: Laura Damian, Oana Antal. Writing- review and editing: Nicolae Cezar Gorcea, Cristina Lenuț, Vasile Bințișan, Liliana Rogoian, Laura Damian, Oana Antal. Supervision: Laura Damian.

## Acknowledgement

Language editing: Mrs. Ioana Robu

## Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## References

- Gaber T, Hahne M, Strehl C, Hoff P, Dörffel Y, et al. (2016) Disentangling the effects of tocilizumab on neutrophil survival and function. *Immunol Res* 64: 665-676.
- Hietbrink F, Bode LG, Riddez L, Leenen LPH, van Dijk MR (2016) Triple diagnosis for early detection of ambivalent necrotizing fasciitis. *World J Emerg Surg* 11: 51.
- Schmitz M, Roux X, Huttner B, Pugin J (2018) Streptococcal toxic shock syndrome in the intensive care unit. *Ann Intensive Care* 8: 88.

4. Ali SZ, Srinivasan S, Peh WCG (2014) MRI in necrotizing fascia of the extremities. *Br J Radiol* 1033: 20130560.
5. Wong CH, Khin LW, Heng KS, Tan KC, Low CO (2004) The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 32: 1535-1541.
6. Nuwayhid ZB, Aronoff DM, Mulla ZD (2007) Blunt trauma as a risk factor for group A streptococcal necrotizing fasciitis. *Ann Epidemiol* 17: 878-881.
7. Hamilton SM, Bayer RC, Stevens DL, Lieber RL, Bryant AE (2008) Muscle injury, vimentin expression and NSAIDs predispose to cryptic group A streptococcal infections. *J Infect Dis* 198: 1692-1698.
8. Bryant AE, Bayer CR, Huntington JD, Stevens DL (2006) Group A Streptococcal Myonecrosis: Increased Vimentin Expression After Skeletal-Muscle Injury Mediates the Binding of Streptococcus Pyogenes. *J Infect Dis* 193: 1685-1692.
9. Pawar AI, Desai RJ, Solomon DH, Ortiz AJS, Gale S, et al. (2019) Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis. a multidata base cohort study. *Ann Rheum Dis* 78: 456-464.
10. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB (2018) Serious infections across biologic-treated rheumatoid arthritis. *Ann Rheum Dis* 77: 905-910.
11. Manabe S, Yanagi H, Ozawa H, Takagi A (2017) Necrotizing soft tissue infection without systemic toxicity in a patient with rheumatoid arthritis treated with tocilizumab. *BMJ Case Rep* 2017: bcr-2017-222826.
12. Yoshida A, Ota T, Sasaoka S, Matsuura H, Fujimoto W, et al. (2012) Necrotizing fasciitis in a patient with rheumatoid arthritis treated with tocilizumab. *Mod Rheumatol* 22: 317-318.
13. Van de Sande MG, van Slobbe-Bijlsma ER (2012) Necrotizing fasciitis in a patient with rheumatoid arthritis treated with tocilizumab. *Rheumatology* 51: 577-578.
14. Hashimoto H, Yamaoka T, Koguchi-Yoshioka H, Tanaka A, Tanemura A, et al. (2015) Development of necrotizing fasciitis in a patient treated for rheumatoid arthritis with tocilizumab. *Acta Derm Venereol* 95: 370-371.
15. Bloomfield M, Parackova Z, Cabelova T, Pospisilova I, Kabicek P, et al. (2019) Anti-IL-6 autoantibodies in an infant with CRP-less septic shock. *Front Immunol* 10: 2629.
16. Isaacs JD, Harari O, Kobold U, Lee JS, Bernasconi C (2013) Effect of tocilizumab on haematological markers implicates interleukin-6 signalling in the anaemia of rheumatoid arthritis. *Arthritis Res Ther* 15: R204.
17. Ribeiro R, Batista F, Paula FS, Alves JD (2019) Changes in Iron Metabolism Induced by Anti-Interleukin-6 Receptor Monoclonal Antibody are Associated with an Increased Risk of Infection. *Pharmaceuticals* 12: 100.
18. Nordqvist G, Walldén A, Brorson H, Tham J (2015) Ten years of treating necrotizing fasciitis. *Infect Dis (Auckl)* 47: 319-325.



- Advances In Industrial Biotechnology | ISSN: 2639-5665
- Advances In Microbiology Research | ISSN: 2689-694X
- Archives Of Surgery And Surgical Education | ISSN: 2689-3126
- Archives Of Urology
- Archives Of Zoological Studies | ISSN: 2640-7779
- Current Trends Medical And Biological Engineering
- International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X
- Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276
- Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292
- Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370
- Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594
- Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X
- Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562
- Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608
- Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879
- Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397
- Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751
- Journal Of Aquaculture & Fisheries | ISSN: 2576-5523
- Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780
- Journal Of Biotech Research & Biochemistry
- Journal Of Brain & Neuroscience Research
- Journal Of Cancer Biology & Treatment | ISSN: 2470-7546
- Journal Of Cardiology Study & Research | ISSN: 2640-768X
- Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943
- Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771
- Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844
- Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801
- Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978
- Journal Of Cytology & Tissue Biology | ISSN: 2378-9107
- Journal Of Dairy Research & Technology | ISSN: 2688-9315
- Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783
- Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X
- Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798
- Journal Of Environmental Science Current Research | ISSN: 2643-5020
- Journal Of Food Science & Nutrition | ISSN: 2470-1076
- Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X
- Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566
- Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485
- Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662
- Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999
- Journal Of Hospice & Palliative Medical Care
- Journal Of Human Endocrinology | ISSN: 2572-9640
- Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654
- Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493
- Journal Of Light & Laser Current Trends
- Journal Of Medicine Study & Research | ISSN: 2639-5657
- Journal Of Modern Chemical Sciences
- Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044
- Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X
- Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313
- Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400
- Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419
- Journal Of Obesity & Weight Loss | ISSN: 2473-7372
- Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887
- Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052
- Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X
- Journal Of Pathology Clinical & Medical Research
- Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649
- Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670
- Journal Of Plant Science Current Research | ISSN: 2639-3743
- Journal Of Practical & Professional Nursing | ISSN: 2639-5681
- Journal Of Protein Research & Bioinformatics
- Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150
- Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177
- Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574
- Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060
- Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284
- Journal Of Toxicology Current Research | ISSN: 2639-3735
- Journal Of Translational Science And Research
- Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193
- Journal Of Virology & Antivirals
- Sports Medicine And Injury Care Journal | ISSN: 2689-8829
- Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: <http://www.heraldopenaccess.us/Online-Submission.php>