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► **To cite this version:**

Elina Zuelgaray, Fanny Domont, Nathan Peiffer-Smadja, David Saadoun, Patrice Cacoub. Tocilizumab-Induced Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome in Adult-Onset Still Disease: A Case Report. *Annals of Internal Medicine*, 2017, pp.141-142. hal-02445328

HAL Id: hal-02445328

<https://hal.science/hal-02445328>

Submitted on 20 Jan 2020

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OBSERVATION

Tocilizumab-Induced Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome in Adult-Onset Still Disease: A Case Report

Background: Adult-onset Still disease is a systemic inflammatory condition characterized by spiking fevers; polyarthritides; and an evanescent, salmon-pink, maculopapular rash. Affected persons have high ferritin levels, a high leukocyte count with neutrophil predominance, and low glycosylated ferritin levels. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor that is used to treat refractory adult-onset Still disease. This drug can cause adverse cutaneous events, such as mild maculopapular rash, urticaria, and pruritus (1).

Objective: To describe what we believe is the first reported case of severe adverse cutaneous effects from tocilizumab.

Case Report: A 55-year-old woman was hospitalized for a 2-month history of spiking fevers, sore throat, arthralgia, evanescent maculopapular rash, leukocytosis (leukocyte count, 23×10^9 cells/L with 89% neutrophils), elevated levels of C-reactive protein (485.7 nmol/L) and ferritin (38 199 pmol/L), and decreased levels of glycosylated ferritin (7%). We excluded infectious diseases and lymphoma and diagnosed adult-onset Still disease.

Therapy with oral corticosteroids and methotrexate was not effective and was replaced with tocilizumab monotherapy, 8 mg/kg. Ten days after the first administration, the patient developed an unusual diffuse, persistent, pruritic maculopapular rash (Figure). Laboratory studies documented a decrease in the levels of C-reactive protein (123.8 nmol/L) and ferritin (7981 pmol/L) and the leukocyte count (14×10^9 cells/L), which suggested improvement. Skin biopsy results showed lymphocyte and eosinophil infiltration in perivascular areas, which supported a diagnosis of a drug-induced reaction. Topical corticosteroids helped alleviate the rash, but laboratory tests 10 days later revealed hypereosinophilia (eosinophil count, 2.3×10^9 cells/L) and liver enzyme levels up to 6 times the upper limit of normal. Polymerase chain reaction testing found a human herpesvirus-6 viral load of 105 copies/mL. We excluded parasitic and blood diseases and diagnosed tocilizumab-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. The new manifestations that we attributed to this syndrome resolved 5 weeks after we discontinued tocilizumab therapy.

Discussion: The dress syndrome is a potentially life-threatening combination of severe skin eruption, fever, hypereosinophilia, and internal organ involvement (2). It typically develops 2 to 6 weeks after initiation of the culprit drug. Manifestations also usually include a morbilliform rash with facial edema, lymphadenopathy, elevated liver enzyme levels, and leukocytosis (2). An immune response to herpesvirus reactivation (human herpesvirus types 6 and 7 and Epstein-Barr virus) is associated with a more prolonged and difficult course. There are few standards for diagnosis of DRESS syndrome,

Figure. Rash that developed 10 d after the first administration of tocilizumab.



which relies on a compatible history and typical clinical manifestations and laboratory results in the absence of other possible conditions.

Diagnosis of this syndrome was difficult because adult-onset Still disease could have caused the patient's elevated liver enzyme levels, leukocytosis, fever, and morbilliform rash. We believe that our diagnosis is justified because the patient did not have abnormal results on liver function tests before initiation of tocilizumab therapy; her new morbilliform rash differed from the previous rash caused by adult-onset Still disease; hypereosinophilia is not a typical feature of adult-onset Still disease; and her usual manifestations of adult-onset Still disease (arthralgia, standard rash, and hyperferritinemia) had remitted when the new symptoms developed, presumably because tocilizumab therapy was successful. Tocilizumab has been proposed as the cause of other adverse cutaneous reactions, including 1 unconfirmed case of Stevens-Johnson syndrome (3), a few cases of psoriasiform eruptions (4), and 1 case of drug-related generalized exanthematous pustulosis (5).

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L16-0592.

doi:10.7326/L16-0592

References

1. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al; OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a

double-blind, placebo-controlled, randomised trial. *Lancet*. 2008;371:987-97. [PMID: 18358926] doi:10.1016/S0140-6736(08)60453-5

2. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124:588-97. [PMID: 21592453] doi:10.1016/j.amjmed.2011.01.017

3. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;387:1921-7. [PMID: 26952547] doi:10.1016/S0140-6736(16)00560-2

4. Sparsa L, Afif N, Bularca S, Fricker A, Thiebault S, Dahan E, et al. [Paradoxical cutaneous reactions associated with tocilizumab therapy]. *Rev Med Interne*. 2014;35:613-6. [PMID: 24630585] doi:10.1016/j.revmed.2014.01.007

5. Izquierdo JH, Bonilla-Abadía F, Ochoa CD, Agualimpia A, Tobón GJ, Cañas CA. Acute generalized exanthematous pustulosis due to tocilizumab in a rheumatoid arthritis patient. *Case Rep Rheumatol*. 2012;2012:517424. [PMID: 23304614] doi:10.1155/2012/517424