SEVERE HYPOFIBRINOGENEMIA IN A PATIENT WITH GIANT CELL ARTERITIS TREATED WITH TOCILIZUMAB: CASE-BASED REVIEW

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Abstract
The Giant Cell arteritis (GCA) is the most common form of systemic vasculitis in elderly patients. The treatment includes high doses of steroids and interleukin (IL)-6 inhibitor tocilizumab, especially in refractory or relapsing disease or in cases where there is an increased risk of steroid-related adverse events. This report discusses the case of a patient with giant cell arteritis who underwent treatment with tocilizumab for four years. The treatment was successful and resulted in clinical remission. However, four years after starting the therapy, the patient developed spontaneous hematomas on their extremities. After further investigation, it was discovered that the patient had developed thrombocytopenia and hypofibrinogenemia, which required substitution therapy. Malignancy and immune-mediated causes of hypofibrinogenemia and thrombocytopenia were ruled out. The patient experienced an extended period of hypofibrinogenemia that lasted for two months after the last dose of tocilizumab. During this time, the levels of CRP remained very low. This could be because the continued inhibition of IL-6 caused impaired hepatic synthesis of acute phase response proteins, which led to low fibrinogen and CRP levels in serum.

The purpose of this case-based review is to emphasize the necessity of regular fibrinogen check-ups in GCA patients treated with tocilizumab.

Keywords: giant cell arteritis; IL-6 inhibitor; tocilizumab; thrombocytopenia; hypofibrinogenemia; FXIII deficiency


Key Messages for Research and Practice

• Tocilizumab linked to severe hypofibrinogenemia and thrombocytopenia and its long-term use associated with gradual decline in fibrinogen and thrombocyte count.

• Tocilizumab disrupts coagulation cascade via IL-6 inhibition.

• There is a need for regular monitoring and caution during treatment.
Introduction

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in elderly patients. It is characterized by granulomatous arteritis that affects large and medium-sized blood vessels with a tendency to affect the cranial arteries [1].

There are three clinical phenotypes of GCA that may overlap: the cranial GCA, large vessel GCA (LV GCA), isolated, and polymyalgia rheumatica [2].

The treatment of giant cell arteritis (GCA) involves high doses of steroids and interleukin (IL)-6 inhibitor tocilizumab. Tocilizumab is especially recommended for refractory or relapsing disease or in cases where there is an increased risk of steroid-related adverse events such as osteoporotic fractures. [3]

Clinical case

We present a 71-year-old female patient with severe hypofibrinogenemia and thrombocytopenia of unknown cause who was admitted to the Department of Rheumatology, Clinical Immunology, and Allergology for further work-up and treatment.

Her medical history was positive for carcinoma at the age of 61. Right-side mastectomy and lymphadenectomy were performed due to breast carcinoma. Subsequently, lymphedema of the right arm developed.

Seven years after mastectomy, the patient developed symptoms of malaise, high fever, and loss of appetite. Her laboratory results revealed elevated ESR, high C-reactive protein (CRP), and anemia. An extensive work-up was performed, infection was excluded, and PET/CT was performed, which excluded malignancy but found elevated metabolic activity characteristic of vasculitis along the aorta and both subclavian arteries. (Fig 1) She was then admitted to the Rheumatology department, and further work-up confirmed the diagnosis of giant cell arteritis. She was treated with high doses of steroids that were gradually tapered, with excellent response. In that period, osteoporosis was confirmed, and she was put on antiresorptive therapy. Two months later, as steroid-sparing therapy, tocilizumab was included at the dose of 162 mg s.c. once weekly, and the steroid was discontinued.

For almost four years, the therapy with tocilizumab was continued. During the follow-ups, she had no signs of illness, and her laboratory results showed normal ESR and CRP, red blood count (RBC), and mildly lower thrombocytes, 107-140 x 10^9/L (referral range 158-424 x 10^9/L). A year after the treatment with tocilizumab was started, control PET/CT was performed with no sign of metabolic activity along arteries. but an aneurysm of the thoracoabdominal and abdominal aorta was described. The patient was referred to a vascular surgeon who concluded that there was no need for surgical intervention and recommended further follow-ups.

The same year, the vertebroplasty of the second lumbar disc was performed due to an osteoporotic fracture.

Two years later, CT angiography showed a fusiform aneurysm of the thoracoabdominal aorta, with a maximum diameter of around 40 mm, and abdominal aorta (35 mm the widest diameter range).

Meanwhile, the patient underwent an endocrinology workup due to elevated serum calcium levels and parathyroid hormone (PTH). SPECT/CT revealed hypermetabolic activity behind the left thyroid lobe, which could be explained as parathyroid gland hyperfunction. Unfortunately, the node was unsuitable for cytological puncture due to its proximity to the aorta. Serum calcium levels were mildly elevated and required no specific treatment, so follow-up was recommended.

Figure 1. PET/CT showing large vessel vasculitis
Due to chronic lymphocytic thyroiditis causing hypothyroidism, levothyroxine was added to the patient’s treatment plan.

4 years after the diagnosis of giant cell arteritis, the patient was examined due to large spontaneous hematomas on the body. Laboratory results revealed an extremely low level of fibrinogen-activity 0.5 g/L (referral range 1.8-3.5), low thrombocytes 74 x 10^9/L (158-424 x 10^9/L), reduced prothrombin time (PT), CRP 0.3 mg/l (>5) and elevated D-dimmers 9355 μg (0-500), so the patient was hospitalized as suspected disseminated intravascular coagulopathy (DIC) of unknown cause. On admission, the patient was feeling well; she had no arthralgia, myalgia, headaches, visual disturbance, or dyspnea; she had a normal body temperature, and her physical exam, besides large leg hematomas and lymphedema of her right arm, was unremarkable (Fig 2).

The patient immediately received a cryoprecipitate transfusion that elevated fibrinogen levels to 1.1 g/L, but there was a remarkable increase in D-dimmers 13,280 μg (0-500).

The next day, there was a decrease in fibrinogen levels and thrombocytes (up to 29 x10^9) with a rise of D-dimmers.

She received cryoprecipitate transfusion first, followed by fibrinogen substitution later in therapy. Tocilizumab was discontinued, and the last dose was administered 4 days before the admission. Steroid boluses and low-molecular-weight heparin (LMWH) were included, but her laboratory results showed no significant improvement.

Extensive work-up was performed: leukocytes and RBC were unremarkable, ESR 1 mm/3.6 KS (5-28), CRP was continuously very low, antinuclear antibody (ANA), ENA, lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein, cryoglobulins, ANCA, RF, anti thrombocyte antibodies, tumor markers, C3, C4, electrophoresis, immunoelectrophoresis, light chains, anti-β2- microglobulin, markers for Hepatitis B, C, Ebstein Barr virus, Cytomegalovirus, Factor (F)II, FV, FVII, FIX; FX, antithrombin, euglobulin clot lysis time, mixing studies plasma, and prothrombin time were unremarkable. Activated partial thromboplastin time (0.76 (0.8-1.2)) and FXIII (0.39 (0.5-20)) were lowered. CT angiography of the aorta showed the progression of a fusiform aneurysm (max diameter 57 mm), and an eccentric mural thrombus was described.

She was examined by a vascular surgeon who recommended thoracic endovascular aortic repair (TEVAR) surgery upon stabilization of the laboratory result.

Initially, DIC was suspected due to suspected malignant disease, but extensive oncological work-up excluded the coexistence of malignancy. On the fifteenth day of hospitalization, she developed cellulitis on the right arm, where lymphedema was previously present. Her laboratory results showed a rise of leukocytes -31 X10^9 (3.4-9.7X 10^9), but CRP remained low – CRP 0.8 mg/L (>5).

From that time on, since there was no expected rise of CRP as a response to acute infection, tocilizumab was suspected to be the main reason for hypofibrinogenemia and thrombocytopenia.

Figure 2. Spontaneous hematomas on the extremities of the patient

The side effect of the drug was reported to the National Agency for Drugs and medical supplies.

Antibiotics were included, steroids were tapered to 1 mg/kg body weight, then to 0.5 mg/kg of body weight gradually, and protective doses of LMWH were continued. There was a prompt resolution of cellulitis.
Four weeks later, her thrombocyte levels gradually improved (to 94 X10(9)), but fibrinogen replacement therapy was still given approximately twice a week (the lowest fibrinogen level during this period was 0.7).

There were no signs of spontaneous hemorrhagic diathesis, so a month after the admission, she was discharged with a recommendation to take prednisone 30 mg and enoxaparin 40 mg s.c daily and regular rheumatological, hematological, and vascular surgeon check-ups.

Four weeks later, after hospitalization, check-up laboratory results showed a significant improvement in thrombocytes at 113 X 10(9), fibrinogen at 1.6, FXIII at 0.61, and D-dimer at 15947 μg/L.

Seven weeks later, fibrinogen rose to 2.3g/L and CRP to 4 mg/l.

Although vascular surgery was recommended, the patient was reluctant toward operation, so two months after hospitalization, she developed pain in the left lumbar region. A vascular surgeon examined her, and a rupture of the aorta aneurysm was diagnosed, but unfortunately, the patient died during the operation.

Search strategy

A literature review was conducted in three electronic databases (PubMed, Scopus, and Web of Science) until December 10th, 2023. Only English-language sources were included, using the terms “Giant cell arteritis” and “tocilizumab,” “hypofibrinogenemia,” “thrombocytopenia,” “Factor XIII,” “Factor XIII deficiency,” “disseminated intravascular coagulopathy,” “large vessel vasculitis,” “interleukin 6 inhibitor interleukin 6,” “coagulation,” in the attempt to identify relevant publications of patients with giant cell arteritis treated with tocilizumab that developed hypofibrinogenemia and thrombocytopenia. The articles were initially chosen based on their title, and the abstract. After that, the full text was examined to ensure it contained relevant content. Priority was given to sources published in the last ten years. Additionally, references cited in the selected articles were manually searched for other relevant articles.

Discussion

Acquired hypofibrinogenemia and thrombocytopenia, such as in our case, are most frequently caused by hemodilution and consumption of clotting factors. This can be seen in various states, such as liver disease, cancer, sepsis with DIC, or as a result of autoantibody formation seen in myeloma or autoimmune disease (e.g., SLE, APS) [4,5,6].

Although tocilizumab was discontinued immediately after the admission, malignancy or autoantibody interference was first suspected in our case.

The investigation ruled out cancer or the coexistence of other autoimmune diseases as the cause of the patient’s condition. However, a crucial turning point in the diagnosis was the failure to respond to acute infection and the subsequent rise of C-reactive protein (CRP) on the 15th day of hospitalization. This led to suspicion that the prolonged thrombocytopenia and hypofibrinogenemia were caused by profound IL-6 inhibition resulting from the administration of IL-6 inhibitor tocilizumab.

Interleukin-6 is a cytokine rapidly produced in infection and tissue injury, but chronic synthesis is present in chronic infection and autoimmune diseases. After IL-6 is initially synthesized in a local lesion, it moves to the liver, where it activates through STAT3 pathway synthesis of acute phase proteins such as CRP, fibrinogen, haptoglobin, etc [7,8,9].

IL-6 also affects various cells besides hepatocytes, such as B and T cells, hematopoietic progenitor cells, megakaryocytes, etc. It directly affects thrombocyte count through megacaryocyte maturation and stimulation, even without other growth factors, causing the elevation of thrombocytes in peripheral blood. [10,11,12]

Mildtocilizumab-induced thrombocytopenias without bleeding events were noted during clinical trials in rheumatoid arthritis, which are included in the drug’s summary of product characteristics (SMPC) [13,14,15].

Lee et al. reported that in their research with RA patients treated with tocilizumab, a low platelet count (mostly mild) was found in 12.3% of patients. The conclusion was that old age is a risk factor for developing thrombocytopenia caused by tocilizumab [16].

There has also been a report of systemic juvenile arthritis (sJIA) patients with thrombocytopenia after tocilizumab administration [17].

In our patient, a mild reduction in thrombocyte count was noted in the medical
history soon after tocilizumab was included in the treatment regime. Still, the worsening was seen during the last hospitalization, when it progressed to a severe form, unresponsive to steroid therapy, which gradually improved in time.

One of the most concerning findings in our patient was severe hypofibrinogenemia. He and the authors found hypofibrinogenemia in 76.5% of sJIA patients (13/17) treated with tocilizumab, with the lowest fibrinogen level below 1.5 g/L in 41% [18].

Marti et al. reported 7 cases of tocilizumab-induced hypofibrinogenemia in patients with rheumatic diseases, one with aortitis among them. In all patients, fibrinogen levels were reduced after a year of treatment. The lowest level of fibrinogen was 0.8 g/L; in that patient, a reduction in FXIII level was noted, with a hemorrhagic event[19].

After four years of receiving tocilizumab regularly, our patient was diagnosed with severe hypofibrinogenemia.

It’s possible that the patient’s fibrinogen level gradually decreased during this period, which was also the case with the thrombocyte count. Unfortunately, the fibrinogen levels were not regularly checked during check-ups until the patient developed signs of spontaneous hemorrhage.

Üsküdar Cansu and the authors presented a GCA patient treated with tocilizumab. The patient developed hypofibrinogenemia, but the side effect was noted one month after the initiation of the therapy, unlike in our patient.

Lower FXIII was also found in our patient. Factor XIIIa is the main stabilizer of the fibrin network at the injury site, preventing premature fibrinolysis, and hemorrhagic events characterize its deficiency [20].

There are several case reports of rheumatic patients treated with tocilizumab who developed FXIII deficiency; one of them was treated with tocilizumab for two years [21,22].

In research conducted by Gualtierotti et al., 15 RA patients were treated with tocilizumab. In responders, there was a significant decrease in CRP and FXIII, with the conclusion that the effect of tocilizumab on FXII is linked to inflammation control, not a direct drug effect [23].

Suri et al. found plasma levels of FXIII-A and FXIII-B significantly lower (by about 25% of normal levels) in tocilizumab-treated RA patients. The mechanism of drug-induced FXIII deficiency is speculated to be due to the down-regulation of FXIII-A synthesis by hematopoietic cells rather than being immune-mediated [24].

There is only one report of a GCA patient treated with tocilizumab who developed combined thrombocytopenia and hypofibrinogenemia, which was also seen in our patient. Still, in this report, FXIII wasn’t mentioned [25].

Our patient experienced a prolonged period of hypofibrinogenemia for about two months after the last dose of tocilizumab. During this time, the levels of CRP remained very low. This could be due to the continued inhibition of IL-6, which caused impaired hepatic synthesis of acute phase response proteins, leading to the inability to elevate serum levels of CRP and fibrinogen, which was best demonstrated when the patient developed cellulitis.

Conclusion

Giant cell arteritis is a common form of vasculitis in elderly patients. Typically, patients with this condition have various comorbidities associated with older age. Therefore, steroid-sparing treatments like tocilizumab are recommended in the treatment plan. Although the treatment is generally safe and effective, caution is necessary. This report highlights its effect on the coagulation cascade and emphasizes the need to screen for hypofibrinogenemia and thrombocytopenia during check-ups regularly.

AUTHORS CONTRIBUTION

All authors made substantial contributions to the article. ŽK, AŠ designed the work, interpreted the data, drafted the paper, and revised it. KFM, AMM, and JMA acquired the data and interpreted and revised it. ŽK wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the anonymization of the patient and for the privacy of individuals who participated in this work. Non-confidential data will be shared with the corresponding author at a reasonable request.
REFERENCES


