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SHORT COMMUNICATION

Etanercept-Associated Transient Bone Marrow Aplasia: A Review of the Literature and Pathogenetic Mechanisms

Natasha Kozak · Joshua Friedman · Ami Schattner

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Abstract A patient with rheumatoid arthritis presented with increasing fatigue, fever, gingival bleeding, and petechial rash. Her symptoms started 1 week after the first injection of etanercept (Enbrel). Her only other medications (methotrexate and hydroxychloroquine) had been unchanged for years. Tests revealed severe pancytopenia and bone marrow aplasia. She recovered with supportive treatment within 12 days. The literature on serious blood dyscrasias associated with anti-tumor necrosis factor-α therapy is reviewed, an intriguing postulated mechanism is discussed, and selective patient monitoring is recommended.

1 Introduction

With the increasing use of agents that block the action of tumor necrosis factor (TNF)-α in the treatment of rheumatoid arthritis (RA) and other chronic immune-mediated inflammatory conditions, recognition of serious adverse events assumes greater importance even when they are rare [1]. We report a patient with RA who presented with transient bone marrow (BM) aplasia associated with the first injection of etanercept, and review the literature on TNF-blocking agent-associated cytopenias.

N. Kozak · J. Friedman · A. Schattner (✉)
Department of Medicine, Kaplan Medical Center, POB 1, Rehovot 76100, Israel
e-mail: amiMD@clalit.org.il

N. Kozak · J. Friedman · A. Schattner
The Faculty of Medicine, Hebrew University and Hadassah, Jerusalem, Israel

2 Report of a Case

A 62-year-old woman was admitted with fatigue, fever (39 °C), gingival bleeding, and a rash over her legs.

She had a history of RA diagnosed 6 years prior when marked synovitis in more than ten large and small joints was found, associated with prolonged morning stiffness, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and strongly positive rheumatoid factor and anti-citrullinated peptide antibodies (250 IU/ml and 76.6, respectively).

Her recent treatment included methotrexate (22.5 mg once a week with daily folic acid) started on diagnosis, hydroxychloroquine (200 mg daily) and a single first injection of etanercept (Enbrel® 50 mg) administered subcutaneously into the thigh 23 days prior to admission.

Previous treatment with leflunomide and adalimumab (Humira®) had failed and been discontinued months before etanercept was started.

No other medications were used, and even methotrexate and hydroxychloroquine were discontinued by her rheumatologist when etanercept was commenced.

One week after the injection, she reported malaise, lassitude, and low-grade fever; those symptoms persisted over 2 weeks.

A sudden appearance of high fever and rash led to her admission.

On admission, she was febrile and tachycardic but stable, with unrewarding examination except for gingival bleeding, a profuse petechial rash over both legs and polysynovitis, which was not new.

Laboratory tests showed hemoglobin (Hb) 7.5 g/dl (normocytic), WBC 1.8×10^9/L with absolute neutrophil count (ANC) 0.7×10^9/L, platelets 3×10^9/L, ESR 172 mm/h, CRP 76.8 mg/dL (normal <6 mg/dL), albumin

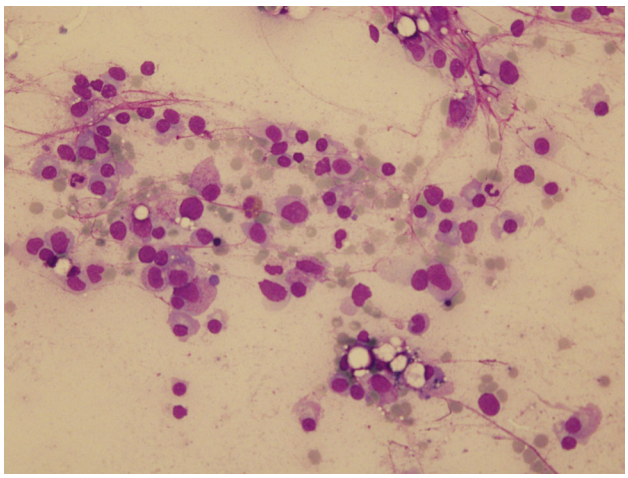

Fig. 1 Patient's bone marrow biopsy showing stroma and plasma cells (more resistant to drug toxicity) but absence of all other hematopoietic elements, consistent with transient aplasia

26 g/L, and globulins 47 g/L (polyclonal). Serum creatinine, electrolytes, and liver enzymes were normal. Peripheral blood smear confirmed severe pancytopenia with absent reticulocytes (0.3 %). Bone marrow aspiration and biopsy revealed BM aplasia (Fig. 1). Methotrexate in serum was undetectable. Chest X-ray, urinalysis, and cultures were normal. Tests for other causes of cytopenias, including serology for Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis viruses, parvovirus B-19, and HIV were negative.

The patient was treated with platelets (four times), packed cells (4 U), granulocyte colony-stimulating factor (Neupogen®) over 5 days, and broad-spectrum antibiotics. She was discharged on the 12th hospital day, afebrile and stable (absolute neutrophil count [ANC] 10.5 $\times$ 10^9/L), for ambulatory follow-up.

One month later, the Hb was 12.4 g/dL, white blood count (WBC) 13.7 $\times$ 10^9/L, and platelets 149 $\times$ 10^9/L. The patient resumed methotrexate treatment uneventfully for more than 6 months of follow-up.

3 Discussion and Review of the Literature

When serious adverse events (SAEs) associated with anti-TNFα therapy are considered, attention is usually focused on an increased risk of infections (in particular, reactivation of tuberculosis and opportunistic infections) and malignancy, though the latter remains an unresolved concern [2].

However, anti-TNFα therapy-induced cytopenias constitute another SAE that are potentially life threatening and mandate better recognition. For example, neutropenia was reported in 14.3–18.8 % of patients receiving a TNFα inhibitor [3–5]. In most of the patients, neutropenia occurred after just 2 weeks of treatment, was mild (mean -1.1 $\times$ 10^9/L), transient, and showed spontaneous resolution, allowing the original treatment to be continued in most (81 %) patients. However, a few patients developed serious secondary infections (4/367, 1.1 %) [5]. Notably, asymptomatic drops in platelet counts (mean -28 $\times$ 10^9/L) were often associated [5]. Indeed, 19 patients with significant thrombocytopenia were identified in a recent review of the literature and, as in the case of neutropenia, almost all were due to either etanercept or infliximab [6]. No other concomitant medication was reported in most of the patients. Rarely, patients may develop both severe neutropenia and thrombocytopenia [7], whereas anemia is not usually a feature of this treatment. On the contrary, with amelioration of the underlying disease on anti-TNFα therapy, the often-present anemia of chronic inflammation frequently improves [8]. However, this therapy, especially etanercept and infliximab, may mediate a more life-threatening adverse event than neutropenia or thrombocytopenia, namely, aplastic anemia and pancytopenia. A few such patients have been identified in post-marketing reports, although the attribution of pancytopenia to the TNF inhibitor remains unclear [9]. The characteristics of all fully reported cases are summarized in Table 1. Thus, etanercept and infliximab have been linked so far to just one case of aplastic anemia each, and several patients had developed pancytopenia or aplastic anemia, which could well have been related to anti-TNFα therapy [11–16]. Most affected patients had RA, and the hematological SAE occurred predominantly after the first TNFα antagonist doses, becoming symptomatic soon after and usually responsive to drug discontinuation and supportive treatment (Table 1).

Our patient presented with symptoms and signs related to all three cytopenias: fatigue (due to anemia); fever that responded to broad spectrum antibiotics (due to severe neutropenia); and petechiae and gingival bleeding (due to severe thrombocytopenia). The absence of concomitant drugs (she had been receiving methotrexate and hydroxychloroquine for years) as well as the temporal relationship between the appearance of her symptoms and the first injection of etanercept, strongly suggest a causal link. Moreover, BM recovery from toxic injury corresponded to the discontinuation of etanercept, whereas methotrexate was later continued uneventfully for months. In contrast, in some of the other cases cited, drugs other than anti-TNFα could have been responsible.

Other than listing all hitherto-reported cases of TNF blocking agent-associated aplastic anemia and pancytopenia, the literature review reveals the rarity of the association, considering that hundreds of thousands of patients have been treated. The other striking feature is

Table 1 Potentially life-threatening non-malignant hematological complications associated with tumor necrosis factor-inhibitor therapy

Patients References	Background	Treatment	Other potential drugs	SAEs	Time interval	Outcome	Remarks
4/367 pts [5]	Varied	Varied	Unlikely	Severe neutropenia with serious infection	NR	Recovered	BM 'normal' in 2 cases
20M [10]	Crohn's spondylarthritis	Infliximab [2nd]	None	Agranulocytosis	NR	Resolved, recurred after retreatment	Granulocyte Bound Ab and neutrophil-specific bound Ab
60F [7]	RA	Infliximab [3rd]	Unlikely	Fever/chills and skin hemorrhages: profound neutropenia and thrombocytopenia	7 weeks	Resolved	BM Bx: hypoplasia
2/61 pts [11]	Juvenile Id. arthritis	Etanercept [1st in 1 pt]	Unlikely	Pancytopenia	0.5; 12 months	Resolved	Open-label prospective study
45F [12]	Scleroderma	Infliximab [1st]	None	Severe pancytopenia and candida peritonitis	3 weeks	Died	Transient HS reaction at 6 days
78M [13]	RA	Etanercept (>17th dose)	Unlikely	Aplastic anemia and sepsis	<3 months	Resolved over 3 weeks	BM Bx+
66M [14]	RA	Infliximab [1st]	Possible	Severe pancytopenia and BM hypoplasia with sepsis	10 days	Resolved over 2 weeks	BM Bx+
32F [15]	Colitis	Infliximab [1st]	Possible (IV ATB)	Severe pancytopenia	6 days	Resolved over 2 weeks	
32NR [16]	Ankylosing spondylitis	Infliximab [1st]	None	Aplastic anemia	4 days	Resolved over 16 days	Associated skin vasculitis BM Bx+
62F Current	RA	Etanercept [1st]	Unlikely	Transient BM aplasia	2 weeks	Resolved over 12 days	BM Bx+

Ab antibodies, *BM* bone marrow, *Bx* biopsy, *F* female, *HS* hypersensitivity, *Id.* idiopathic, *IV ATB* intravenous antibiotics, *M* male, *NR* not reported, *pt(s)* patient(s), *RA* rheumatoid arthritis, *SAE* serious adverse event, + postive

the complexity of the pathogenesis. TNFα is a pleiotropic cytokine, part of a complex cytokine network that regulates hematopoiesis and may affect BM stem cells differently under different circumstances [17, 18]. On one hand, TNFα (and interferon γ) are overexpressed in the BM of patients with acquired aplastic anemia and can be involved in BM stem cell apoptosis and suppression of erythropoiesis [19, 20]. Thus, treatment with TNFα antagonists can be a useful approach to the treatment of refractory aplastic anemia [21–23]. On the other hand, under different conditions, TNFα interacting with other cytokines directly enhances the clonal growth of BM progenitors and suppresses hematopoietic stem cell apoptosis [17, 24]. Thus, its blockade can also exert a deleterious effect on hematopoiesis [6]. Since autoimmune mechanisms are believed to have a key role in the pathogenesis of idiopathic aplastic anemia [25], the association between TNF-targeted therapies and induction of autoimmune diseases (particularly, vasculitis and lupus predominantly with infliximab and etanercept) is also a tenable mechanism [26].

In conclusion, TNFα antagonists for the treatment of RA show significant benefit and are generally safe in comparison with other disease-modifying anti-rheumatic drugs [27–29]. BM suppression resulting in severe cytopenia, transient pancytopenia, or aplastic anemia is a well established but fortunately rare SAE of anti-TNFα therapy. Since a steadily increasing number of patients are being treated for longer periods, any serious adverse effect, however rare, may be encountered.

Monitoring blood counts of patients starting treatment seems advisable, and we also suggest that patients should be instructed to consult their physician when unexplained fever, fatigue, or bleeding manifestations appear.

Conflict of interest The authors confirm that they have no conflict of interest in connection with this manuscript.

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