

Acquired Erythrocytosis Upon Treatment with Infliximab for Ankylosing Spondylitis

To the Editor:

We describe a patient with ankylosing spondylitis (AS) who was treated with infliximab and developed polycythemia that was Janus kinase 2 (JAK2)-negative (V617F and exon 12 mutation). This is the first report of a patient with AS that developed erythrocytosis on treatment with infliximab.

A 31-year-old man of Italian and German ethnicity with HLA-B27-positive AS was started on treatment with infliximab (5 mg/kg dose) in May 2007 because of lack of response to nonsteroidal antiinflammatory drugs. The disease showed excellent response to infliximab. He had a 15-pack-year smoking history. Prior to starting infliximab, in April 2007 his hemoglobin was 14.5 g/dl, hematocrit 45.5%, and platelet count $334 \times 10^3/\mu\text{l}$. He gradually developed erythrocytosis (June 2008) with hemoglobin 20.3 g/dl, hematocrit 56.6%, and platelet count $218 \times 10^3/\mu\text{l}$, and was referred to the hematology clinic in July 2008. His peripheral blood smear was noted to be benign. Jak2 mutation was negative including exons 12/14, and erythropoietin level was normal. Bone marrow biopsy revealed erythroid hyperplasia and a mild increase in reticulin staining. He was started on aspirin and therapeutic phlebotomies until his hematocrit decreased to 43.6%, and it has remained below 45% after 12 months of phlebotomies with continued treatment with infliximab.

Polycythemia is suspected in men when hematocrit rises above 52% or hemoglobin concentration above 18.5 g/dl; the corresponding values for women are > 48% hematocrit or > 16.5 g/dl hemoglobin. Polycythemia can be classified as primary or secondary. Elevated levels of erythropoietin are observed in secondary polycythemia. Most often, this is a response to hypoxia, but can also result from an erythropoietin-secreting tumor. Evidence has suggested that smoking tobacco results in higher red cell mass or decreased plasma volume caused by high carboxyhemoglobin levels². Since our patient had normal levels of erythropoietin, secondary polycythemia was an unlikely diagnosis.

A Janus kinase 2 gene (*JAK2*) encodes a cellular tyrosine kinase crucial to cell signaling for erythropoiesis as well as other myeloproliferative processes. The JAK2 protein requires erythropoietin molecules to dimerize and signal erythroid precursor cells, on which JAK2 lies, to go forward with erythrocyte production³. It has been found that *JAK2* mutations, specifically *JAK2* V617F exon 14 mutation that replaces a phenylalanine for a valine at position 617, permit the JAK2 protein to malfunction. This mutation acquired after birth results in JAK2 proteins that do not require erythropoietin to signal red cell production; thus, *JAK2* mutations allow erythropoiesis to proceed unchecked. This mutation is associated with 95% of patients with polycythemia vera^{3,4,5,6,7}. Other molecular alterations located on JAK2 exon 12 have been described in 50%–80% of the JAK2 wild-type polycythemia vera⁸. Our patient tested negative for both the mutations on JAK2 exon 12 and exon 14.

Infliximab is a chimeric IgG1k monoclonal antibody targeted against tumor necrosis factor- α (TNF- α). It is now used in the treatment of various inflammatory diseases including AS¹, rheumatoid arthritis (RA), ulcerative colitis, Crohn's disease, psoriasis, and psoriatic arthritis. Hematologic dyscrasias associated with infliximab toxicity include leukopenia, neutropenia, thrombocytopenia, and pancytopenia. Centocor, the manufacturer and distributor of infliximab in the United States, was contacted and there were no reports of erythrocytosis, polycythemia, myelofibrosis, or elevated red blood cell count in their research or postmarketing database.

We suggest a possible mechanism through which infliximab could cause erythrocytosis based on a review of the literature (Figure 1). There is increasing evidence that cytokines such as TNF- α , interleukin 1 (IL-1), IL-6, and interferon- γ are involved in inflammatory diseases. TNF- α has 2 opposing destructive and protective functions on a cell. TNF binds to 2 cell-surface receptors (TNFRI and TNFRII) located on hematopoietic cells, as well as on many other cells. After binding, TNFRI mediates the destructive effect of TNF- α through activation of a cascade leading to cell death.

It also mediates cell protection through a pathway involving nuclear factor- κ B (NF- κ B). TNFRII (which lacks a death domain) interacts with TNF receptor-associated factor 2 (TRAF-2). TRAF2 activates both NF- κ B and JNK, mediating an anti-apoptotic effect (Figure 1). Bone marrow of patients with RA shows significant increase in TNFRI and a mild increase in TNFRII. TNF specifically inhibits macrophage iron release and as well inhibits the formation of early red cell colonies in bone marrow⁹. In addition it has a key role in inducing and sustaining tissue damage by activating the inflammatory cascades as well as stimulating angiogenesis. Bone marrow of patients with RA shows significant increases in TNFRI and mild increases in TNFRII that can cause angiogenesis^{10,11} (Figure 1). Details of this proposed mechanism remain to be determined.

Studies in RA show that there is increased production of TNF- α in the bone marrow that leads to anemia of chronic disease because of apoptotic deletion of hematopoietic progenitor cells, or by stimulating production of inhibitory cytokines by bone marrow accessory cells¹¹. Therapy with infliximab improves manifestations of RA as well as the anemia of chronic disease by significantly increasing the hemoglobin level even while patients are receiving methotrexate¹². Dose-related improvements in anemia have been noted upon anti-TNF therapy in patients with RA; these findings suggest that TNF- α has an effect on erythroid development^{12,13}. Similarly, it has been reported that patients with myelodysplastic syndromes (MDS) have increased TNF- α expression in bone marrow progenitor cells; erythropoiesis is downregulated in these patients¹⁴. A study has shown that patients with MDS treated with infliximab may experience an increase in hemoglobin¹⁴. It may be that when TNF- α expression in the bone marrow is suppressed, an erythrocytosis may ensue, as in our patient. It has been documented in patients with AS that anemia of chronic disease improves from baseline with infliximab¹⁵. But ours is the first report of a patient with AS that developed erythrocytosis on treatment with infliximab. We found no published reports of secondary erythrocytosis in patients with other diseases treated with infliximab.

It is important to recognize the consequences of erythrocytosis left untreated. In a study of polycythemia vera, the incidence of vascular thromboses was found to be 41% (over 20 years) and the overall mortality was 2.9% per year¹⁶. The recommendation for secondary erythrocytosis is phlebotomy to reduce the hematocrit to 45% if hematocrit is > 54%¹⁷. The European Collaboration on Low-dose Aspirin in polycythemia vera (ECLAP) study established the therapeutic benefit of aspirin in polycythemia vera¹⁸, which significantly reduced the risk of nonfatal thromboembolic events or death from cardiovascular causes.

Our case experience supports a possible association between infliximab therapy and secondary erythrocytosis, and we propose a mechanism of such an association. It is important that rheumatologists and hematologists recognize this association in order to identify this potentially detrimental effect and initiate appropriate treatment.

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REFERENCES

1. Aitchison R, Russell N. Smoking — A major cause of polycythaemia. *J R Soc Med* 1988;81:89-91.
2. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005;365:1054-61.

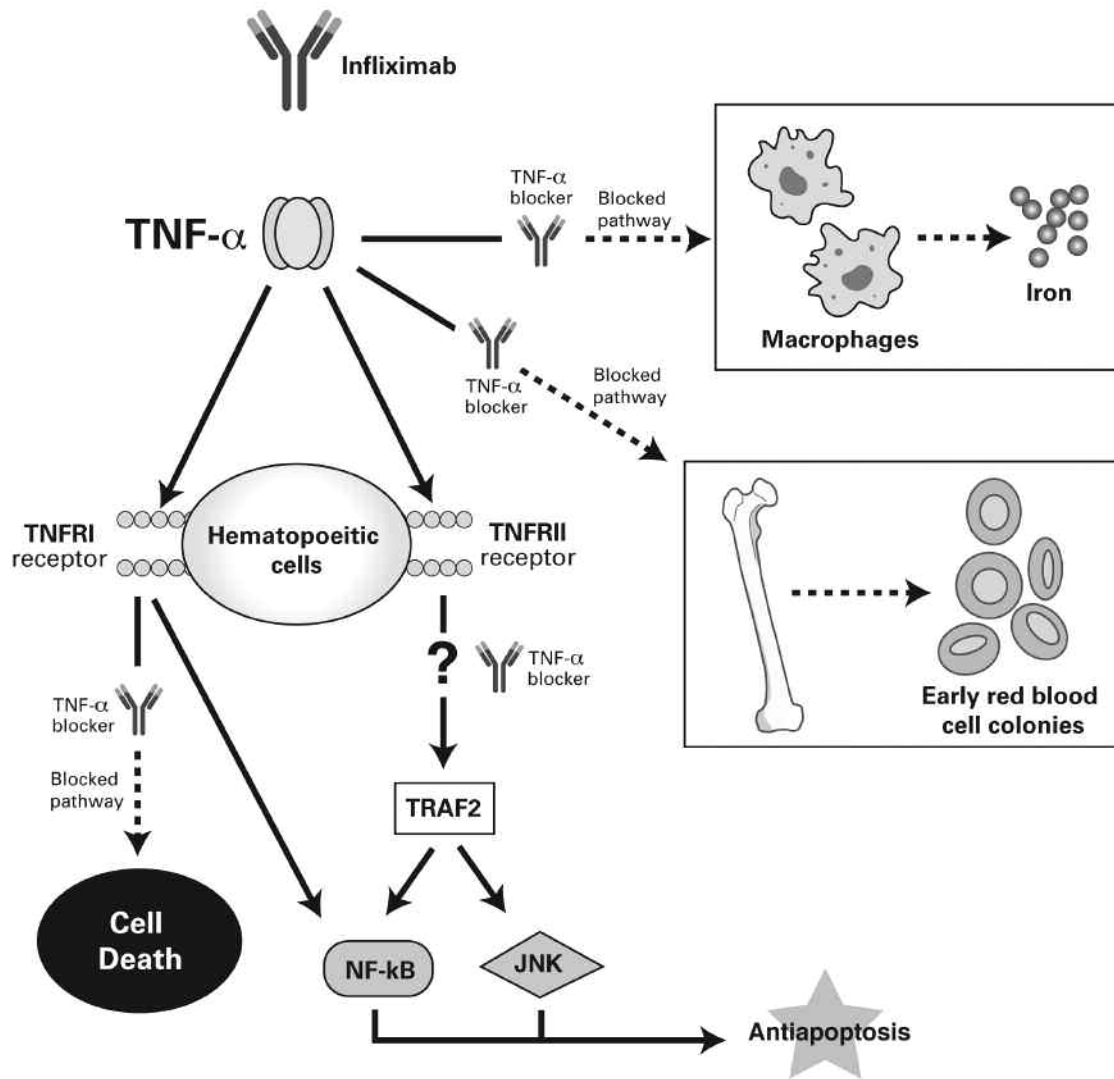


Figure 1. A possible mechanism through which infliximab could cause erythrocytosis.

- Tanabe N, Ohnishi K, Fukui H, Ohno R. Effect of smoking on the serum concentration of erythropoietin and granulocyte-colony stimulating factor. *Intern Med* 1997;36:680-4.
- Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* 2005;7:387-97.
- James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. *Nature* 2005;434:1144-8.
- Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med* 2005;352:1779-90.
- Scott LM, Tong W, Levine RL, Scott MA, Beer PA, Stratton MR, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med* 2007;356:459-68.
- van der Heijde D, Dijkmans B, Guesens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; 52:582-91.
- Davis D, Charles PJ, Potter A, Feldmann M, Maini RN, Elliott MJ. Anaemia of chronic disease in rheumatoid arthritis: in vivo effects of tumor necrosis factor alpha blockade. *Br J Rheumatol* 1997;36:950-6.
- Sawanobori M, Yamaguchi S, Hasegawa M, Inoue M, Suzuki K, Kamiyama R, et al. Expression of TNF receptors and related signaling molecules in the bone marrow from patients with myelodysplastic syndromes. *Leuk Res* 2003;27:583-91.
- Papadaki HA, Kritikos HD, Valatas V, Boumpas DT, Eliopoulos GD. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor-alpha antibody therapy. *Blood* 2002;100:474-82.
- Aalto K, Honkanen V, Lahdenne P. Iron status during anti-TNF therapy in children with juvenile idiopathic arthritis. *Clin Rheumatol* 2010 Sept 30 [Epub ahead of print].
- Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor

- (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
14. Stifter G, Heiss S, Gastl G, Tzankov A, Stauder R. Over-expression of tumor necrosis factor-alpha in bone marrow biopsies from patients with myelodysplastic syndromes: relationship to anemia and prognosis. *Eur J Haematol* 2005;75:485-91.
 15. Braun J, van der Heijde D, Doyle MK, Han C, Deodhar A, Inman R, et al. Improvement in hemoglobin levels in patients with ankylosing spondylitis treated with infliximab. *Arthritis Rheum* 2009;61:1032-6.
 16. Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. *Ann Intern Med* 1995;123:656-64.
 17. McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, Hunt B, et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005;130:174-95.
 18. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med* 2004;350:114-24.
- J Rheumatol* 2011;38:3; doi:10.3899/jrheum.101013