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<RH>Letter to the Editor

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Myelodysplasia in a psoriasis patient receiving etanercept: Cause or coincidence?

Sir,

Myelodysplastic syndrome comprises hemopoietic insufficiency, often associated with cytopenias of one or more cell lineages that may lead to leukemic transformation.[1] Here, we report a case of myelodysplastic syndrome in a psoriatic patient following therapy with tumour necrosis factor-α blocking agent (etanercept).

A 76-year-old male patient presented with psoriasis vulgaris since the last 20 years without any arthritis. He was treated with subcutaneous etanercept, 50 mg twice a week for 6 months followed by once a week for another 6 months, to achieve Psoriasis Area and Severity Index 90 (PASI90) at 6 months. Prior to etanercept he had been treated with topical steroids, topical vitamin D analogues, 6-month course of narrow-band-ultraviolet-B and 1-year acitretin without any appreciable benefit.

After one year of etanercept therapy, the patient presented to our emergency unit with spontaneous bluish bruising (ecchymosis) and recurrent epistaxis. A complete blood count recorded critically low platelet count (23×10^9/L), anemia (11.7 g/dl) and normal leukocyte count (6.6×10^9/L), with 0.5×10^9/L monocytes and 2% blasts [Figure 1]. Reticulocyte count was 136×10^3 cells/mm^3, 3.4% (N = 0.8–2.5%) with low reticulocyte index, serum ferritin was

1280 ng/ml (*N* = 21.8–274.7 ng/ml) and folate was low at 1.7 ng/ml (*N* = 7–31.4 ng/ml), which indicated ineffective erythropoiesis. (Table 1)

Bone marrow aspirate [Figure 2] and biopsy [Figure 3] revealed hypercellularity. Blast cells accounted for almost 8% of the total nucleated marrow cells. The majority of neutrophils were hypogranular. Hypolobulated megakaryocytes were observed. Reticulin fibres were not increased.

Peripheral blood also revealed bicytopenia, blasts and 0.5×10^9/L monocytes. Bone marrow showed 8% trilineage dysplasia and blasts. A diagnosis of myelodysplastic syndrome with excess blasts-1was made based on the hematologic picture.

We stopped etanercept treatment and administered two cycles of azacitidin and folic acid supplementation, with almost no response and even worsening of platelet count (17×10^9/L) and hemoglobin (8.3 g/dl). While he was waiting for the third cycle, he was admitted to the emergency unit suffering from lower gastrointestinal bleeding, epistaxis and shock. The patient expired eventually due to cardiopulmonary arrest.

Immune dysregulation and altered T-cell hemostasis are essential factors for the development of myelodysplastic syndrome. Several authors have reported a higher risk of myelodysplastic syndrome in patients suffering from autoimmune disorders, resulting from chronic overproduction of apoptosis inducing cytokines like tumor necrosis factor-alpha. It has been proven that accelerated apoptosis of bone marrow cells accounts for the disturbed hemopoiesis and peripheral blood cytopenias leading to myelodysplastic syndrome, despite the presence of hypercellular bone marrow.[1] In addition, nonspecific activation and proliferation of T

lymphocytes seen in myelodysplastic syndrome has been documented to promote epidermal growth in genetically susceptible psoriasis patients.[2]

Myelodysplastic syndrome may be associated with psoriasis in about 7% of cases.[3] Özbek *et al*. reported a 3.5-year-old girl with psoriasis, hypogammaglobulinemia and pancytopenia who developed myelodysplastic syndrome-excess blasts that progressed to acute myeloid leukemia.[2] Moreover, Maleszka *et al*. noted increased incidence of leukemia and laryngeal cancer among families of psoriasis patients.[4] In addition, there are some reported cases of leukemia that developed in psoriasis patients receiving systemic immunosuppressives (cyclosporine, methotrexate and etanercept). However, the association of leukemia and psoriasis is not well-investigated.[4]

Etanercept may induce various hematological side effects including pancytopenia and aplastic anaemia, as reported by the US Food and Drug Administration.[5] Tumor necrosis factor-alpha enforces apoptosis of tumor cells and promotes different antitumor activities like activation of natural killer cells, stimulation of CD8 cells and acceleration of camptothecan and etoposide antitumor effect. Loss of such activities may mediate tumor growth in acute and chronic myeloid leukemia.[6]

Tumor necrosis factor-alpha is also inhibitory to hematopoietic stem cells. Studies have shown increased levels of tumor necrosis actor-alpha in myelodysplastic syndrome marrow. Thus, antagonizing it significantly enhances *in-vitro* hematopoietic colony formation. Deeg *et al*. tried to treat myelodysplastic syndrome with etanercept as a pilot trial.[7] However, their study found limited favorable response in some patients and worsening of blood cell counts in others. The findings of Deeg *et al*. and the contradictory effects of tumor necrosis factor-alpha on dysplastic

bone marrow suggest that tumor necrosis factor-alpha is only partially accountable for the dysregulated hemopoiesis in myelodysplastic syndrome; thus there are various other pathomechanisms for myelodysplastic syndrome.[7]

Only three cases of myelodysplastic syndrome have been reported till date in psoriasis patients following etanercept therapy, ours being the 4th case. Nair *et al*. reported the case of a 57-year-old man with psoriatic arthritis who developed myelodysplasia that progressed to acute myeloid leukemia after 6 months of etanercept treatment.[6] Bachmeyer *et al*.[8] and Knudson *et al*.[9] reported the cases of 40 and 43-year-old psoriatic males who were diagnosed with myelodysplastic syndrome after 4 and 14 months of etanercept therapy, respectively. The case reported by Knudson *et al*. had progressed to acute myeloid leukemia followed by death.[9] In addition to the aforementioned cases, another case was reported by Bakland and Nossent where a 31-year-old female with ankylosing spondylitis developed acute myeloid leukemia 4 months after etanercept treatment.[5] In our case, myelodysplasia with excess blasts developed 1 year after initiating etanercept therapy.

Taken together, the current case adds to the growing evidence that suggests a link between myelodysplastic syndrome and etanercept treatment in psoriasis patients. Pre-treatment thrombocytopenia was seen in our patient (131×10^9/L) and the patient reported by Knudson *et al*. patient (126×10^9/L)[9], while mild leucopenia (3.6×10^9/L) was reported by Bakland and Nossent before initiation of etanercept.[5] More studies are needed to clarify whether this was an accidental association or etanercept may aggravate myelodysplasia in all susceptible patients.

Although progressive and critical worsening of blood counts following etanercept treatment may demonstrate its aggressive hematologic and myelodysplastic adverse events, the susceptibility of

psoriasis patients to myelodysplasia cannot be ruled out. Therefore, the present case and literature review support the need for pharmacovigilance, prospective cohort or retrospective case-control studies to prove or disprove this association.

In conclusion, psoriatic patients being treated with etanercept should be considered at dual risk of developing myelodysplastic syndrome – therapy-related and autoimmunity-associated. Hence, we recommend that psoriatic patients who are receiving etanercept should be followed regularly by routine blood counts and it should be discontinued upon onset of any cytopenias.

<H2>Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his ~~images and other~~ clinical information to be reported in the journal. The patient understand that name and initials will not be published ~~and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.~~

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<H2>Conflicts of interest

There are no conflicts of interest.

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Table

Table 1: Retrospective analysis for complete blood count of the reported case

CBC (reference range and unit)	**Baseline**	**During etanercept treatment**		**After stoppage of etanercept**		
				1 month	**With use of azacitidine**	
		6 months	**12 months**		**2 months**	**4 months**
Hemoglobin (14.0–18.0 g/dl)	17.6	15.8	11.7	11.0	9.2	8.3
White blood cells (3.0–11.0×10^9/L)	9.4	6.0	6,6	21.0	9.0	7.3
Neutrophils (2.0–7.0×10^9/L)	6.5	4.0	4.9	16.0	6.8	3.8
Lymphocytes (1.0–3.0×10^9/L)	1.1	0.9	0.9	2.5	0.9	1.7
Monocytes (0.2–1.0×10^9/L)	1.2	0.9	0.5	0.8	0.9	0.9
Eosinophils (0.02–0.5×10^9/L)	0.01	0.0	0.0	0.0	0.0	0.03
Basophils (0.02–0.1×10^9/L)	0.64	0.2	0.1	1.3	0.2	0.65

Blast (0.0×10^9/L)	0.0	0.0	0.1	0.4	0.2	0.2
Platelet (150–450×10^9/L)	131	70	23	23	17	17
CBC: Complete blood count						

Figure Legends

Figure 1a: Peripheral blood smear showing monocytes (black arrow) (×100)

Figure 1b: Peripheral blood smear showing blast cells (red arrow) (oil immersion) (×100)

Figure 2: Bone marrow smear showing hypercellular bone marrow with hypolobated megakaryocytes (arrow and inset × oil immersion) (×~~400~~ 40)

Figure 3: Bone marrow trephine biopsy showing hypolobated megakaryocyte (red arrow) and a cluster of abnormal localization of immature precursors (blue arrow) (×~~400~~ 40)