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Marrow Suppression with Myelodysplastic Features, Hypoerythropoetinemia, and Lipotrophic Proptosis Due to Rosiglitazone

Derek E. Clevidence, MD, PhD; Mark B. Juckett, MD; Mark J. Lucarelli, MD

ABSTRACT
Thiazolidinediones (TZDs) are frequently used pharmacotherapeutics for type II diabetes mellitus, which exert their effect through peroxisomal proliferator agonist receptor (PPAR) mediated increased insulin sensitivity. TZDs are known to cause marrow suppression and to stimulate adipogenesis. Case and cohort studies show TZDs worsen thyroid-associated orbitopathy. We present a case consistent with earlier reports of marrow suppressive pancytopenia manifesting as myelodysplastic syndrome, a new implication of hypoerythropoetinemia, and non-Graves’-associated proliferative proptosis.

CASE
A 60-year-old retired nurse presented in January 2007 with the diagnoses of uncomplicated type II diabetes mellitus, myelodysplastic syndrome (MDS), and chronic conjunctivitis. For the preceding 2 years she was treated with darbepoetin (Aranesp) for MDS-associated anemia. She received episodic gentamicin sulfate and steroid ophthalmic drops for conjunctivitis. She was distressed with the prognosis of MDS and also complained of progressive eye irritation, ocular pain, and proptosis.

Type II diabetes was diagnosed in 1997 and was well controlled with metformin 1000mg daily, diet, and exercise. Rosiglitazone (Avandia) 4 mg twice daily was added to her regimen in 2004, and her hemoglobin A1C remained below 6.5%.

A screening complete blood count (CBC) in 2005 was remarkable for new-onset anemia and mild leukopenia. Her workup for anemia in 2005 included laboratory, gastrointestinal, genitourinary, and hematologic studies. Chronic gastritis and a gastric polyp were reported by esophagoduodenoscopy. Capsule endoscopy diagnosed angiodysplasia of the jejunum was followed by fulguration. Colonoscopy showed a hyperplastic rectal polyp, which was removed. Fecal occult blood tests were negative. Pelvic ultrasound and a screening uterine D&C were normal/negative. Slight homocysteinemia (15 umol/L [reference <12umol/L]) with normal methylmalonic acid, vitamin B12, and folate levels was an incidental finding. She was treated with injected and then oral vitamin B12 without improvement in her anemia. A bone marrow biopsy in 2005 was interpreted as having normal cellularity with mild dyserythropoiesis, dysmegakaryopoiesis, a myeloid left shift, and morphological findings suspicious for an early myelodysplastic syndrome. Also, ringed sideroblasts were elevated, but the percentage was insufficient for the diagnosis of a sideroblastic anemia. The clinical and pathological findings were felt to be most consistent with MDS, and the patient was started on darbepoetin with a rapid response to therapy. She was treated for gastroesophageal reflux and chronic gastritis with omeprazole, started multivitamin supplementation, and was maintained on a regimen of darbepoetin.

Her past medical history was otherwise notable for an isolated episode of ulcerative colitis during college, but no recurrences. She also suffered perimenopausal depression, hyperlipidemia, insomnia, and asymptomatic episodic tachycardia initially diagnosed postpartum. She had no history of kidney disease. Surgical history included the above studies, Cesarean section, cholecystectomy, appendectomy, and tonsillectomy.
were normal, including peripheral pulses. There was no edema or sign of fluid excess in particular. The abdomen was obese with normal bowel sounds, no hepatosplenomegaly, tenderness, or bruits. Genitourinary exam was normal. The musculoskeletal exam was normal. There were no rashes or suspicious lesions on skin exam. Neurologic exam revealed no deficits or evidence of peripheral neuropathy.

Her lab results on presentation in 2007 were remarkable for anemia and leukopenia (neutropenia) with normal platelets. Comprehensive metabolic panel, thyroid stimulating hormone (2.00 uIU/mL [0.34-4.82 uIU/mL]), free T4 (1.48 ng/mL [0.7-1.8 ng/mL]), thyroid stimulating immunoglobins (109% [0-129%]), anti-thyroid antibodies, vitamin B12, and anti-nuclear antibody screen were all normal range. Hemoglobin A1C was 6.1%; erythrocyte sedimentation rate was 37mm/hour (<20 mm/hour); and homocysteine was 14 umol/L (4-10 umol/L). Erythropoietin level was inappropriately low at 12mU/ml (reference range 4-27 mU/ml in setting of normal hematocrit) (Table 1). Bone marrow biopsy was repeated in 2007 that showed mild hypercellularity due to erythroid hyperplasia, megaloblastic changes in the erythroid lineage, but no dysplastic changes in the myeloid or megakaryocytic cells. Cytogenetic analysis were normal, including peripheral pulses. There was no edema or sign of fluid excess in particular. The abdomen was obese with normal bowel sounds, no hepatosplenomegaly, tenderness, or bruits. Genitourinary exam was normal. The musculoskeletal exam was normal. There were no rashes or suspicious lesions on skin exam. Neurologic exam revealed no deficits or evidence of peripheral neuropathy.

She was menopausal in 1999 and had no post-menopausal bleeding episodes and no abnormal Pap smears. She smoked three-quarters of a pack cigarettes per day for 30 years and quit in 1996. She denied drug or alcohol use. Exercise capacity was limited by fatigue symptoms. Family and social history were noncontributory otherwise.

Medications throughout 2007 included rosiglitazone 4 mg twice daily, episodic gentamicin 0.3% ophthalmic drops, episodic ocular steroid drops twice daily, atenolol 50 mg daily, gemfibrozil 600 mg twice daily, metformin 1000 mg daily, bupropion 150 mg twice daily, triazolam 0.25 mg as needed for sleep, and darbepoetin (Aranesp). Allergies were reported to tetracycline, erythromycin, penicillin, sulfa, and clindamycin (all causing hives); and iodinated intravenous (IV) contrast.

Physical exam showed a pleasant woman of her stated age with normal range vital signs except for weight 95 kg (body mass index=34.9). Ocular findings included bilateral conjunctival injection and proptosis. Anterior rhinoscopy showed a healed perforation at the proximal septum. Oropharynx was noted for dental restorations. Palpation of the neck revealed no lymphadenopathy, thyromegaly, or nodules. Auscultation was negative for thyroid or carotid bruits. Cardiac and pulmonary exams were normal, including peripheral pulses. There was no edema or sign of fluid excess in particular. The abdomen was obese with normal bowel sounds, no hepatosplenomegaly, tenderness, or bruits. Genitourinary exam was normal. The musculoskeletal exam was normal. There were no rashes or suspicious lesions on skin exam. Neurologic exam revealed no deficits or evidence of peripheral neuropathy.

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Table 1. Complete Blood Count Results Over Time

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>White blood cell count</td>
<td>4.0-11.0/10.3/mL</td>
<td>7.9</td>
<td>3.2b</td>
<td>2.2b</td>
<td>2.8b</td>
<td>6.0</td>
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<tr>
<td>Red blood cell count</td>
<td>4.20-5.40/10.6/uL</td>
<td>4.58</td>
<td>3.58b</td>
<td></td>
<td></td>
<td>4.2</td>
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<tr>
<td>Hemoglobin</td>
<td>12.0-16.0/g/dL</td>
<td>13.6</td>
<td>10.0b</td>
<td>11.6b</td>
<td>12.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.0-48.0/%</td>
<td>40.1</td>
<td>33.2b</td>
<td>38</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>80.0-100.0/Fl</td>
<td>87.6</td>
<td>92.7</td>
<td>93</td>
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<td></td>
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<tr>
<td>Mean cell hemoglobin</td>
<td>27.0-32.0/pg</td>
<td>29.7</td>
<td>27.9</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration</td>
<td>32.0-36.0/g/dL</td>
<td>33.9</td>
<td>30.1b</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red cell distribution width</td>
<td>11.5-16.5/%</td>
<td>12.4</td>
<td>15.9</td>
<td>13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>150-450/10.3/uL</td>
<td>291</td>
<td>219</td>
<td>204</td>
<td>237</td>
<td>250</td>
</tr>
<tr>
<td>Mean platelet volume</td>
<td>7.4-10.4/Fl</td>
<td>10.4</td>
<td>10.8b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>40.0-75.0/%</td>
<td>44.7</td>
<td>44.1</td>
<td>38b</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>15.0-45.0/%</td>
<td>43.5</td>
<td>40.4</td>
<td>44</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.0-15.0/%</td>
<td>6.6</td>
<td>10.7</td>
<td>11</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>1.0-3.0/%</td>
<td>3.4b</td>
<td>3.2b</td>
<td>5b</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.0-3.0/%</td>
<td>1.8</td>
<td>1.6</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>1800-8750 /uL</td>
<td>1411b</td>
<td>840b</td>
<td>1630</td>
<td>3320</td>
<td></td>
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<tr>
<td>Absolute Lymphocyte Count</td>
<td>675-4950 /uL</td>
<td>1293</td>
<td>990</td>
<td>630</td>
<td>1780</td>
<td></td>
</tr>
<tr>
<td>Absolute Monocyte Count</td>
<td>0-1650 /uL</td>
<td>342</td>
<td>250</td>
<td>460</td>
<td>470</td>
<td></td>
</tr>
<tr>
<td>Absolute Eosinophil Count</td>
<td>40-330 /uL</td>
<td>102</td>
<td>110</td>
<td>60</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>Absolute Basophil Count</td>
<td>0-330 /uL</td>
<td>51</td>
<td>50</td>
<td>40</td>
<td>80</td>
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</table>

Note: Initial complete blood count results with baseline comparison from May 21, 2003. The white blood count (WBC) nadir was 2.2 K/mL with an absolute neutrophil count 840/uL while the hemoglobin was stable at 11.6g/dL on darbepoetin and platelets were 204K/uL. The last dose of rosiglitazone was in the first week of February 2008 and no darbepoetin was given in February 2008. The next blood count revealed the normal hemoglobin, and 3 weeks later the WBC had normalized, then remained at the 5/2008 levels.

a Indicates different laboratory reference range without impact on interpretation.

b Abnormal result.
Rosiglitazone is a highly selective PPAR-gamma agonist whose downstream effects increase insulin sensitivity in adipose tissue, skeletal muscle, and liver. One of the principal mechanisms of TZD action appears to be the promotion of adipocyte proliferation and triglyceride accumulation. TZDs are known to increase subcutaneous, but not visceral, fat to increase fluid retention; and to exacerbate heart failure.

Anemia in the setting of TZD therapy is thus usually attributed to dilution secondary to increases in plasma volume rather than to decreased cell number. GlaxoSmithKline’s package insert reports decreases in mean hemoglobin during clinical trials occurred in a dose-related fashion in adult patients by up to 1 g/dL. No difference between combination and mono-therapy was noted. The insert also reports white blood cell counts decreased slightly in adult patients, but this finding is not specified further. Maaravi and Stessman presented a case linking rosiglitazone to pancytopenia in a dose-dependent fashion (hemoglobin 14.4 to 12.3 g/dL on supramaximal [12 mg/day] dosing), which reversed on discontinuation. Symptomatic isolated anemia (hemoglobin 9.8 g/dL) has also been reported in a patient taking rosiglitazone 4 mg twice daily. A placebo-controlled trial using pioglitazone demonstrated mild hematologic changes not explainable by volume changes. Fibric acids, including gemfibrozil and fenofibrate, activate PPAR-alpha and may also be associated with pancytopenia. Fatty transformation of the bone marrow was a concerning possibility early in TZD development but has not been known to occur at standard doses.

PPAR-gamma is also a positive transcriptional auto-regulator in at least orbital and subcutaneous fat tissue and is critical to adipocyte differentiation. Thiazolidinediones (TZDs) are ligands for nuclear receptors called peroxisome proliferator activated receptors (PPARs). Their molecular biology and history are reviewed by Yki-Järvinen. The PPAR signaling pathway effects changes in a variety of cellular processes including proliferation, metabolism/energetics, and inflammation.

Ophthalmic consultation indicated the periorcular findings were suggestive of thyroid eye disease. Key findings consistent with Graves’ ophthalmopathy included conjunctival chemosis, engorgement of the medial rectus insertions on external exam, lower lid retraction, and severe symmetric proptosis with Hertel measurements of 28 mm OU. An orbital magnetic resonance imaging (MRI) in fall 2007 showed a predominance of periorcular fat, but not other abnormalities (Figure 1).

Because of the concern that rosiglitazone may be contributing to both proptosis and low hemoglobin, it was discontinued. After discontinuing rosiglitazone, her hemoglobin normalized within 3 weeks, followed by the leukocytes. The proptosis due to adipose hypertrophy has partially improved, and the patient reported less ocular pressure and relief of pain within 3 months. Her hemoglobin A1C remains unchanged.

DISCUSSION

Thiazolidinediones (TZDs) are ligands for nuclear receptors called peroxisome proliferator activated receptors (PPARs). Their molecular biology and history are reviewed by Yki-Järvinen. The PPAR signaling pathway effects changes in a variety of cellular processes including proliferation, metabolism/energetics, and inflammation. Rosiglitazone is a highly selective PPAR-gamma agonist whose downstream effects increase insulin sensitivity in adipose tissue, skeletal muscle, and liver. One of the principal mechanisms of TZD action appears to be the promotion of adipocyte proliferation and triglyceride accumulation. TZDs are known to increase subcutaneous, but not visceral, fat to increase fluid retention; and to exacerbate heart failure.

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PPAR-gamma is also a positive transcriptional auto-regulator in at least orbital and subcutaneous fat tissue and is critical to adipocyte differentiation. Orbitopathic changes have been previously reported in patients treated with rosiglitazone. Lee and colleagues report a case of stable thyroid associated orbitopathy in a 56-year-old female smoker with Graves’ disease, whose orbitopathy flared after starting rosiglitazone. Apparent non-thyroid rosiglitazone associated proptosis was first reported by Levin in 2005. A later study by Dorkhan in 2006 supported these conclusions. This 6-month open label prospective study of 36 patients treated with pioglitazone found eye protrusion of at least 2 mm in 13, even in the absence of detectable thyroid disease. Particularly notable in this series was identification of 3 risk factors for greater than 2 mm proptosis: thyroid disturbance (Graves’ disease, subclinical hyperthyroid, subclinical hypothyroid, autoimmune hypothyroidism, or nodular goiter); low

Figure 1. Magnetic resonance images of orbits. (A) T1 pre-contrast axial image at level of optic nerve and (B) T1 fat suppressed post-contrast coronal image showing muscle insertions. Bilateral proptosis with prominence of the orbital fat and normal appearance of the extraocular muscles, globes, and optic nerve.
adiponectin (independent of thyroid status); and pioglitazone dose.16

Our patient experienced marked hematologic changes on standard doses of rosiglitazone not associated with detected volume overload or preexisting anemia. Although abnormalities were discovered on extensive gastrointestinal (GI) evaluation, interventions did not lead to normalization of her hemoglobin or explain her leukopenia. Furthermore, the possibility of occult GI bleeding as cause of anemia is inconsistent with the finding of persisting neutropenia. The finding of a normal or hypercellular marrow with depressed peripheral blood counts indicates ineffective hematopoiesis which is the hallmark of MDS. Although she did not have definitive morphological changes of MDS, the megaloblastic changes, presence of ineffective hematopoiesis, and clinical findings were felt to be most consistent with this diagnosis. However, the rapid recovery after discontinuation, and the absence of fatty replacement of bone marrow on biopsy, is most consistent with marrow suppression secondary to rosiglitazone therapy. Unique to this case was the finding of an inappropriately low erythropoietin level and improvement of her anemia with darbepoetin, which suggests a secondary inhibition of erythropoietin release from the kidney.

Her proptosis developed in the absence of thyroid abnormalities, and to a degree greater than the baseline reported in the pioglitazone study.16 The MRI finding of abundant periorbital fat tissue is consistent with rosiglitazone stimulated adipogenesis and triglyceride accumulation in a manner previously described.12

Since these effects may occur in a dose-dependent manner, it is possible the coadministration of gemfibrozil with rosiglitazone led to increased levels of the latter. Coadministration of gemfibrozil and rosiglitazone does increase rosiglitazone levels,5 but this combination would still not be expected to exceed the maximal dosing for rosiglitazone. Moreover, the combination of PPAR-alpha agonism by gemfibrozil and PPAR-gamma agonism by rosiglitazone may have been synergistic. Next generation TZD-class medications with combined PPAR pathway targeting may reveal similar patterns of adverse reactions. Our patient’s proptosis and marrow suppression could also be due to variance in xenobiotic metabolism, PPAR receptor mutations, receptor co-factor changes, or response element mutations. Each is testable.

In addition to concern for fluid expansion and heart failure exacerbation, this case adds evidence that clinicians who manage diabetes should consider TZD therapy as a possible cause of marrow suppression and proptosis. These risks may be amplified in the setting of overt or subclinical thyroid dysfunction and may be exacerbated further by drug interactions, particularly with fibrates. Future research in human pharmacogenomics holds promise to identify individuals who may be more likely to have these adverse effects. In a more general sense, this case illustrates the need for clinicians to keep an open mind about causality when seemingly unrelated conditions present in an unusual way.

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REFERENCES
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