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CLINICAL VIGNETTE

Case Report of Improvement of Psoriasis with Pioglitazone

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Case Report

A 65-year-old female presents to a primary care clinic for follow-up on her chronic medical conditions including poorly controlled type 2 diabetes mellitus (DM) and psoriasis. She has suffered from diabetes for the past 12 years. Despite diet and exercise, she remains wheelchair-bound and has lost only 6 pounds in the last year. For control of her advanced diabetes, she was taking Humulin-N 50/24 daily, pioglitazone 15 mg daily, sitagliptin 50 mg daily, and repaglinide 2 mg 3 times a day. The patient was previously taking rosiglitazone but was changed to pioglitazone due to possible cardiac complications. Interestingly, the patient reports that her psoriasis has markedly improved in the past 2 months with no active symptoms except for a rash under her breasts. Her physical examination was unremarkable except for the presence of morbid obesity and an erythematous rash in her inframammary fold region that appeared irritated with a white crust but no visible scaling. Since a spontaneous remission of a genetic, life-long disease like psoriasis without explanation is uncommon, this warranted further investigation of factors that might have treated the skin disorder that the patient and physician were unaware of.

Psoriasis is an immune-mediated disorder of hyperproliferation and abnormal differentiation of the epidermis¹. Grossly, the lesions have a characteristic, sharply demarcated erythematous, silvery scaling appearance. On a cellular level, the abnormal affected areas contain an inflammatory infiltrate with increased cytotoxic T lymphocytes and elevated cytokine levels. Like many other immune-mediated diseases, psoriasis has been shown to have a genetic predisposition with environmental triggers. These include infection or physical and/or emotional stressors that preceded the onset of the disease. It has been suggested that psoriasis may be associated with certain HLA types. Smoking, alcohol consumption, and obesity are all correlated with the incidence of psoriasis, but a direct causal relationship has not been established. However, the incidence of psoriasis is directly proportional to BMI, suggesting a dose-dependent relationship².

Psoriasis has a prevalence rate of 2% and is more common in Caucasians than in African Americans or Asians¹. It affects men and women equally with a bimodal distribution of peak incidence, once at 20 to 30 years of age and then at 50 to 60 years of age. Although psoriasis is seemingly rare according to its reported prevalence rate, this can be deceiving because many mild cases of psoriasis go undiagnosed or unreported. Additionally, the types of psoriasis can manifest in very different ways. Plaque psoriasis is the most common type and is characterized by chronic erythematous scaling plaques in the classic and symmetric distribution on the scalp, extensor elbows, knees, and back. Inverse psoriasis refers to the same plaques but in the opposite distribution more centrally prevalent in the intertriginous areas, often presenting without visible scaling. Psoriasis can also involve the nails and joints and can be quite deforming and debilitating in severe cases. Lastly, there is an uncommon form of life-threatening psoriasis which manifests as inflammatory pustules that can appear acutely or chronically known as pustular psoriasis.

An association between psoriasis and diabetes mellitus has been noted and is currently being studied. A direct causal relationship between these two diseases has not been established, but a correlation between the two has been postulated. A retrospective case-control study in Israel showed a higher incidence of diabetes in psoriatics as compared to the general population (odds ratio 1.27, $P < 0.05$). However, this study could not distinguish between type 1 and type 2 diabetes. Due to the immune nature of the disease, this correlation might be deceiving because type 1 DM is more often associated with auto-immune disorders than type 2 DM³. Although the etiology of their coexistence is unclear,

it is not uncommon for a patient with psoriasis to present with concurrent diabetes due to the worldwide prevalence of diabetes. Therefore, a medication that could address both glycemic control and psoriasis would be extremely useful in many ways, including cost-control, reducing pill burden, and providing an alternative option to non-responsive psoriasis.

The preferred method of treatment for psoriasis depends on the severity of the disease¹. Mild disease is usually treated with topical agents, including steroids and emollients. These are sometimes combined with limited sun exposure, either via light box under physician supervision or outside of the office. The UV radiation present in sunlight can act as a natural immunosuppressive that is both convenient and cost-effective for the patient. However, care must be taken to avoid sunburn because that might induce Koebner's phenomenon where new epidermal injury could cause the psoriasis to worsen rather than improve. Moderate to severe psoriasis usually requires systemic immunosuppressive therapy. Options include steroids, calcineurin inhibitors, phototherapy, methotrexate, and biologic agents. The introduction of biologic agents has brought the preferred first-line treatment for psoriasis under debate. It remains controversial whether a patient should be started on a biologic agent initially or should first exhaust less effective alternative treatments with fewer side effects and less cost.

A new class of medications has recently been introduced in the treatment of diabetes mellitus known as the thiazolidinediones or glitazones. Thiazolidinediones' main mechanism of action is through activation of the peroxisome proliferators-activated receptor γ (PPAR γ)⁴. Through their binding of the PPAR γ , thiazolidinediones have an insulin sensitizing effect, stimulating peripheral glucose metabolism and redistribution of fat stores from the viscera to subcutaneous stores. They are used for glycemic control, as well as for anti-proliferative⁵ and anti-inflammatory purposes⁶. Specifically, the binding of thiazolidinediones to PPAR γ has been shown to decrease the activity of inflammatory cytokines,⁷ particularly TNF- α . Such properties have been postulated as the basis for the improvement seen in psoriatics taking the thiazolidinediones.

The first report of a thiazolidinedione used for psoriasis came from a small 3-patient open-label study. All 3 patients had psoriasis and poorly-controlled diabetes that were unresponsive to traditional treatment. Their psoriasis could not be continually treated with high-dose steroids due to the effects on their glycemic control. Following administration of troglitazone for 10 to 25 weeks, all 3 patients reported significant improvement in their psoriatic lesions, which did not occur while they were taking sulfonylureas or biguanides⁸. Another case reported was of a 65-year-old man with concomitant diabetes and psoriasis who was placed on pioglitazone 150 mg/day for glycemic control and experienced "complete remission of psoriasis."⁹ Subsequently, a myriad of case reports and small short term trials consisting of 1 to 7 patients describing the therapeutic benefits of glitazones on psoriasis, improving both the patients' subjective observations of their condition as well as the physicians' objective reportings of their patients' progress, have been published.

To further investigate the above-described effects of glitazones on psoriasis, tissue cultures were taken from psoriatics and infiltrated with troglitazone. This showed normalization of the skin. When the psoriatic skin specimens were transplanted onto Severe Combined Immunodeficiency (SCID) mice treated with oral troglitazone, the lesions exhibited improvement with decreased thickness, less inflammation, and showed differentiation¹⁰. At one point, it was thought that a topical form of the glitazones might be a beneficial form of treatment. However, clinical trials using topical 0.5% rosiglitazone to treat plaque psoriasis showed no promising clinical results with no impact on the patients' Psoriasis Area of Severity Index (PASI) scores¹¹.

Despite the failed topical therapy, systemic thiazolidinedione regimens are still being explored. A 10-week, double-blind, randomized, placebo-controlled, parallel-group study of 70 patients was conducted to evaluate the response of moderate to severe psoriasis when given oral pioglitazone. This study showed a dose-dependent improvement of the disease while receiving pioglitazone, with a "percent reduction in mean PASI scores of 21.6%, 41.4%, and 47.5% in the placebo, pioglitazone 15 mg, and [pioglitazone] 30 mg groups, respectively". Most of the improvements occurred after 6 weeks of taking the drug, suggesting that a prolonged course of therapy would be necessary to achieve clinical

results¹². However, rosiglitazone was studied in 2 large, randomized, double-blinded studies where it performed no better than placebo in reducing the PASI score¹³. Currently, this topic is still controversial and the thiazolidinediones are not formally considered a treatment for psoriasis.

Although thiazolidinediones were originally introduced and marketed as diabetic drugs, they were discovered to also have anti-inflammatory properties that coincidentally benefited other concomitant immune diseases present in the diabetic patients. This has led to the investigation of other possible pharmacologic benefits that the glitazones have to offer in psoriasis and many other inflammatory diseases. Despite the many promises that this new class of medication has to offer, there is still conflicting data and concern over other adverse effects these drugs can have. Troglitazone was taken off the market shortly after its introduction because of the paradoxical liver dysfunction, sometimes leading to liver failure⁴. Additionally, there has been some apprehension in using rosiglitazone because of a recent study suggesting an increased risk of cardiovascular events and death with its use¹⁴.

In today's world of medicine facing an aging population with an epidemic of obesity, diabetes mellitus, and heart disease, the development of new pharmaceutical drugs has been the focus of targeted therapy. With increasing comorbidities, the sickest patients have complicated multi-drug regimens. Simplification of daily medications has been shown to improve patient compliance, and the possibility of treating 2 diseases with a single agent is very appealing. Unfortunately, sulfonylureas, biguanides, and alpha-glucosidase inhibitors have not been shown to have any effect on psoriatic disease when studied in comparison to the glitazones¹⁵. It was by chance that thiazolidinediones were discovered to have a beneficial effect in psoriatics, and this observation merits further research to realize the full potential of the glitazones.

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