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CASE REPORT

Combined Dopaminergic Drugs to Treat Pyoderma Gangrenosum

Jerome H Check[1,2]* and Diane L Check[2]

[1]Cooper Medical School of Rowan University, Camden, NJ, USA
[2]Cooper Institute for Reproductive Hormonal Disorders, Mt Laurel, NJ, USA

Abstract

Monoclonal antibody therapy directed against certain pathways leading to the eventual cellular immune reaction to an irritating agent has been a mainstay of therapy for many pathological conditions considered autoimmune in nature. Unfortunately, these monoclonal antibody therapies are extremely expensive, and may lead to some serious adverse complications e.g., risk of infection or developing cancer based on generalized immune suppression, and other less common adverse effects that may be quickly lethal. Some of these autoimmune conditions may over time show a greater frequency of other types of autoimmune pathology. For example, patients with rheumatoid arthritis and inflammatory bowel disease may develop subsequently certain autoimmune skin disorders e.g., pyoderma gangrenosum. Interestingly dopamine agonists have been found to very effectively ameliorate rheumatoid arthritis, inflammatory bowel disease, and many autoimmune skin disorders that previously failed to respond adequately to these other biological immunosuppressants A case of a 51-year-old woman with a long history of rheumatoid arthritis had failed to respond adequately to immune suppression with high dosage, glucocorticoids and could not tolerate either Etanercept or Adalimumab. However, for many years, her joint pain and fatigue were markedly improved following treatment with the dopamine agonist dextroamphetamine sulfate. After many years on dextroamphetamine, she developed pyoderma gangrenosum, which not only failed to improve despite two courses of infliximab, but unfortunately she had a very severe reaction to the drug. She did have marked improvement, however, with the addition of another dopamine agonist carbidopa levodopa. The hypothesized mechanism of action of dopamine agonists is to correct tissue permeability defects, thus inhibiting irritating agents from crossing the mucosal barrier leading to severe inflammation.

***Corresponding author(s)**

Jerome H Check, Cooper Medical School of Rowan University, Camden, NJ, 7447 Old York Road, Melrose Park, PA 19027, USA, Tel: +215-635-4400; Fax: +215-635-2304
Email: megan.oneil@ccivf.com

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Introduction

Pyoderma gangrenosum is a rare condition that is seen more commonly in patients with a history of autoimmune diseases or oncologic conditions, e.g. acute myelogenous leukemia or

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myelodysplasia [1-4]. The disorder manifests with the quick development of skin lesions especially on the lower legs that most often appear as open sores. It may have started initially as a small bump [5]. Though most frequently seen in the legs, ankles, and feet, it can occur anywhere in the body, especially if there has been a recent wound or a surgical procedure. These lesions are generally very painful [5].

Though a lesion may develop from a cut, the etiology is not considered to be infectious but rather of an obscure autoimmune nature [2]. Nevertheless, one possible complication is to develop an infection from an open sore. The condition is more common in women from early childhood to middle age. The autoimmune conditions most associated with developing pyoderma gangrenosum are ulcerative colitis, Crohn's disease, and rheumatoid arthritis [2].

Mild cases of pyoderma gangrenosum may just have one ulcer, or there may be many ulcers in patients with severe cases. With severe cases, sometimes treatment with silver sulfadiazine skin cream may help to prevent secondary infection. Severe cases may warrant immunosuppressive therapy, e.g., mycophenolate, cyclosporine, or tumor necrosis alfa inhibitors, e.g., adalimumab, and infliximab [1]. In some instances, hyperbaric oxygen may be required. Pyoderma gangrenosum may take many weeks or even months to finally heal [1].

Case Report

A 51-year-old woman suffered from painful joints and fatigue for over 20 years related to rheumatoid arthritis. She previously had severe side effects from both etanercept and adalimumab. She was never treated with infliximab. She did not have much relief from non-steroidal anti-inflammatory drugs or methotrexate. Thus, for 10 years she was treated with a moderately high dosages of prednisone. The prednisone only gave her a modest improvement in the joint pain and only slight improvement in her fatigue.

Unfortunately, she had significant side effects from the chronic use of prednisone requiring a partial jaw replacement and shoulder surgery related to osteonecrosis and osteoporosis. She sought an opinion from our center, and we placed her on amphetamine salts 30mg twice daily providing 37.6mg of the active ingredient dextroamphetamine sulfate. This provided much better relief of pain. Thus, she was able to reduce her prednisone to just 5mg per day, and the pain was now very tolerable. Just as important, she had marked improvement in her fatigue. This improvement continued for 10 years.

One other complication from the previous high dosage glucocorticoid treatment was very thin skin which was easily bruised and cut with minimal trauma. She required wound care for many of the cuts she received in the last 6 years. When traumatic cuts on both shins were not healing well, she developed ulcerative lesions on both shins which were more painful than her cuts. Since these ulcer-like lesions were worsening over a quick period, she consulted a top dermatologist at a major teaching university hospital. Both by observation and confirmed by biopsy, she was diagnosed with pyoderma gangrenosum.

Awaiting the results of the biopsy there was another two-week delay in treatment. Though this dermatologist was advised of the previous severe adverse reactions to etanercept and adalimumab, he still recommended a trial with infliximab. This woman who had been inflicted with severe pain for 40% of her life, which never incapacitated her, now developed such severe pain in both legs that she could no longer walk. Actually, the pyoderma gangrenosum lesions worsened by appearance 1 week from the infliximab injection. She was admitted to that same university hospital for further evaluation and treatment.

The cause of the severe pain was not apparent. The dermatologist favored that the clinical picture was consistent with a local infection possibly even osteomyelitis. However, the infectious disease specialists disagreed, since they were unable to detect any infection. Nevertheless, with no other diagnosis they treated her with a variety of intravenous antibiotics. However, the pain was not ameliorated at all. She was discharged on opiates and oral antibiotics. Her stay in the hospital was two weeks. Despite the apparent severe reaction to infliximab, the dermatologist insisted that this was not an adverse side effect of infliximab. His view was that the pyoderma gangrenosum lesions were the cause of the "infection" that he believed was the source of pain so that it was of paramount importance to eradicate the pyoderma gangrenosum lesions for her to get better. Thus, he gave her one more infusion of infliximab the day of discharge from the hospital.

Her pain in her shin was extremely intense within 24 hours of taking the second course of infliximab. The pain intensified to such a degree that she now described it as excruciating. Opiates did not provide much, if any, relief. She said her only method for slight relief would be to keep screaming as loud as she could.

When in the hospital they did not continue the amphetamine salts. Her hope was that resuming dextroamphetamine sulfate would alleviate the pain. The amphetamines did help her fatigue and reduced the joint pain, but the excruciating shin pain continued, and the sores remained open and weeping.

She returned to our office hoping that an increase in her dosage could improve her pain. However, for unknown reasons, this very well tolerated and highly effective amphetamine therapy that is not addicting in the dosages used has class II narcotic restrictions and seems to concern pharmacists and insurance carriers. We were concerned that raising the dosage of the amphetamine salts could jeopardize the pharmacists continuing to fill the prescription for the 60mg dosage of amphetamine salts. This, we suggested that she add carbidopa levodopa 10/100mg twice daily. Similar to amphetamine salts, carbidopa levodopa is another dopamine agonist.

Within 2 weeks she had marked improvement of her shin pain, and the pyoderma gangrenosum lesions were almost healed. At the 2-week mark of treatment with the combination of the 2 dopamine agonist drugs, she did not think that any analgesics were needed anymore. Nevertheless, because she had been on higher dosages of opiates for a prolonged period of time, she was advised to gradually reduce the dosage to prevent withdrawal symptoms.

Though clinically continuing her marked reduction of pain and healing of the pyoderma lesions, and even though she gradually reduced the dosage of opiates, she was found unconscious. Consideration was given to the possibility that the unresponsiveness was related somehow to an opiate overdose. Thus, she was given naloxone. She responded to it and woke up shortly after the naloxone was given. She was admitted to a different university hospital closer to her home for observation. She was found to be in acute renal failure. Since this eventually spontaneously remitted, the probable etiology was considered to be a rare complication of infliximab causing renal artery thrombosis. Failing to clear the opiates through renal excretion was considered to be the likely cause of narcotic overdosage despite the reduction in dosage.

Other complications ensued while hospitalized, including a stroke. She subsequently developed many other pathological events while hospitalized. This eventually led to her death after 4 weeks in the hospital. It should be noted that while hospitalized the physicians

did not continue either the amphetamine salts or the carbidopa-levodopa. Though the pyoderma lesions returned, the severe leg pain did not return, suggesting that the severe pain following the infliximab injection was not from the pyoderma lesions per se. rather the severe leg pain was considered possibly as another complication of infliximab. The possibility of microvascular thrombosis in the legs with resulting ischemia was one of the considerations for the cause of the leg pain.

We are purposely presenting this case report at this time before the results of an autopsy are provided to strictly discuss the beneficial effect of dopamine agonists for pyoderma gangrenosum. This case shows that not only do dopamine agonists have greater efficacy than these immunosuppressive drugs, (at least in some cases) but are much safer and much less likely to lead to lethal adverse events.

Discussion

One of the first case reports related to taking a dopamine agonist for treating a skin disorder was published in 1984 showing great efficacy in resolving severe chronic treatment resistant urticaria [6]. The marked beneficial efficacy of dopamine agonists for chronic urticaria was confirmed by subsequent publications [7-9].

There had been several publications related to other dermatologic or neuro-dermatologic chronic pathological conditions that are resistant to "standard" therapy that have responded very well to dopamine agonists including eczema, keratosis pilaris, cutaneous discoid lupus erythematosus, bullous pemphigoid, palmoplantar eczema, generalized puritus without lesions, dystrophic epidermolysis bullosa, lichen sclerosis, and erythromelalgia [10-18]. Furthermore dopamine agonists have ameliorated problems with mucus membranes e.g., recurrent apthous stomatitis [19,20].

The use of dopamine agonists for not only these dermatologic conditions but many other chronic disorders is based on the hypothesis that the basis for most chronic conditions is related to increased cellular permeability leading to the infusion of unwanted irritants into various tissues leading to inflammation and subsequent pain. Inflammatory tissue damage could even lead to possible eventual organ damage or physiological dysfunction related to mitochondrial dysfunction or neurological disorders [21-24].

This concept developed from hypothesizing that in view of the similarity of cancer and the fetus, i.e. rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, possibly studies evaluating the mechanism of how the fetal placental semi-allograft accomplishes these feats could lead to novel ways to treat cancer [25,26]. There is evidence that one of the critical steps for successful implantation is the need to quickly develop spiral arteries in the luteal phase which have cell walls that are only one cell thick to allow nutrient exchange between mother and fetus. Evidence supports the hypothesis that the development of spiral arteries is accomplished by an autoimmune stripping off of the thick cell walls of some of the uterine arteries developed during the proliferative phase. To bring cellular immune cells into the endometrium to accomplish the uterine artery remodeling evidence suggests that the secretion of progesterone can inhibit the effect of dopamine in diminishing cellular permeability allowing the infusion of irritants across the mucosal barrier [27,28]. This could explain why certain conditions e.g., pelvic pain or headaches, may be more common premenstrually. However, the increased tissue permeability may be present in women throughout the menstrual cycle and in males also [22-24,29-32].

Dopamine agonists have been found to markedly improve rheumatoid arthritis and other type of joint or muscle and ligament pain as well as chronic fatigue [33-41]. The dopamine

agonist dextroamphetamine sulfate did provide significant relief for the patient described here for her arthritic pain and fatigue for many years before she developed the pyoderma gangrenosum.

As mentioned, because of years of treatment with prednisone, she had very thin skin and did not heal quickly. Initially she thought that she must have injured her shins. However, with worsening of the pain, and the development of the ulcers on both shins, she appropriately consulted a dermatologist. She did not ask our opinion whether she should take the infliximab treatment. Most likely related to her past history of severe adverse events following treatment with other tumor necrosis factor alpha inhibitors, we would have recommended to first try to either increase her dosage of dextroamphetamine sulfate, or stay at the same dosage, but add another dopamine agonist drug. She did ask our opinion as to whether she should take a second course of the infliximab. We strongly suggested not to take the second course because of the very severe reaction she had to the first course. Nevertheless, somehow, the dermatologist convinced her to take the second course which we think ultimately led to a cascade of pathologic adverse events leading to her death.

Though dextroamphetamine was well tolerated. We have seen more terminal pathological conditions not responding to standard therapy, respond to very high dosages of amphetamine without side effects [42,43]. However, she was concerned that the pharmacist would not fill his/her prescription if we raise the dosage because of previous comments from the pharmacist. We have seen that the combination of dextroamphetamine and another dopamine agonist cabergoline can effectively improve painful pathological entities e.g., the burning mouth syndrome (Stomatodynia). However, we chose to keep her at the 60mg dosage of amphetamine salts and add carbidopa levodopa(10-100mg) because we have found the latter to be a more effective drug for the increased cellular permeability syndrome (a name we coined for the general condition) when comparting the efficacy to other dopamine agonists [44,45]. Indeed, the pain markedly improved with the combination of dextroamphetamine sulfate and carbidopa levodopa and the pyoderma gangrenosum lesions were practically gone.

Conclusion

This case suggests that pyoderma gangrenosum can be added to the long list of chronic dermatological conditions that are frequently refractory to standard medications but yet respond to dopamine or dopamine agonists. This is not the first case where autoimmune conditions have failed to respond to tumor necrosis alpha inhibitors but demonstrate a quick, very positive response to dopamine agonists. Dopamine agonists are much safer than immunosuppressant therapy. Dopamine agonists have ameliorated quickly the symptoms of many autoimmune conditions that failed to respond to monoclonal antibody immunosuppressants. Dopamine agonists are far less expensive than monoclonal antibody type of immunosuppression. Dopamine agonists also have much less side effects than glucocorticoids [46-51].

Conflict of Interest:

None

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