Marked improvement of intractable arthritic pain in a woman with rheumatoid arthritis with sympathomimetic amine treatment despite previous failure with standard therapy and possible implications for last trimester unexplained fetal demise - case report

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Summary

Purpose: To determine if sympathomimetic amine treatment could alleviate severe arthritic pain and fatigue associated with rheumatoid arthritis which was refractory to other medical therapy in a patient with a history of unexplained last trimester fetal demise and unexplained cessation of fetal movement and acidosis. *Methods:* A 32-year-old female was treated with 10 mg of dextroamphetamine sulfate daily after failing to gain relief with standard therapy for rheumatoid arthritis. *Results:* After several weeks of therapy the patient noticed fewer flare ups of arthritic pain and a marked improvement in her fatigue. Six months on the sympathomimetic amines she noticed improvement in her ability to carry out everyday activities, less flare ups, and increased energy. *Conclusions:* Sympathomimetic amines as demonstrated in this case report can effectively relieve joint pain when conventional therapies for rheumatoid arthritis fail, at least if the water load test is abnormal. Perhaps this therapy could prove beneficial in inhibiting chorionic villitis which can cause fetal death.

Key words: Idiopathic edema; Arthritis; Fetal demise.

Introduction

Rheumatoid arthritis is a chronic, inflammatory autoimmune disease affecting the joints as well as the rest of the body. In patients with this disorder the immune system is triggered to recognize "self" proteins, such as the synovium between the joints, as foreign, and attacks, destroys and releases cytokines to recruit inflammatory mediators to these sites [1]. The inflammation associated with rheumatoid arthritis is an ongoing process of increased capillary permeability at the site of inflammation, increased blood supply, recruitment of leukocytes to the site, and release of inflammatory cytokines. The cytokines released in rheumatoid arthritis such as interleukin 1 (IL-1), IL-12, tumor necrosis factor (TNF)-alpha, and interferon (INF)-gamma are to initiate a TH1, T-cell mediated immune response as well as activate matrix metalloproteinases which mediate destruction of cartilage, extracellular matrix, tendon, and bone [1, 2]. As a result of chronic inflammation, the patient experiences swelling around the joints as well as stiffness and pain which can be severe. This process will eventually cause permanent disfiguring of joints as inflammatory mediators break down the cartilage between the bones and bone remodeling occurs. Patients with rheumatoid arthritis are treated with a variety of therapies such as non-steroidal anti-inflammatory drugs (NSAIDS), or corticosteroids which reduce the production of prostaglandins and reduce inflammation. Other therapies include methotrexate and other cytotoxic drugs which interfere with the metabolism of rapidly proliferating inflammatory cells, and antibodies against cytokines such as TNF-alpha or cytokine receptor antibodies.

Many autoimmune diseases such as rheumatoid arthritis remit during pregnancy but exacerbate or have onset after pregnancy. This is due to the effect of progesterone on the immune system during pregnancy especially with the expression of a progesterone-induced blocking factor (PIBF) which is a 34 kDa protein expressed by gamma/delta T cells that had de novo progesterone receptors induced by the allogeneic stimulus of the fetus [3]. Progesterone-induced blocking factor suppresses natural killer (NK) cell cytolytic activity and causes a shift from TH1 cytokines which favor the cellular immune system to TH2 cytokines which favor the humoral immune system [4].

The case study presented here describes a woman diagnosed with rheumatoid arthritis based on having a positive rheumatoid factor and arthritis who had unexplained sudden last trimester fetal death in her second pregnancy and near sudden fetal death in her third. Her failure to gain relief from her arthritis with standard immunosup-

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pression therapy for rheumatoid arthritis but her quick response to therapy aimed at inhibiting vascular permeability has to make one think that increased vascular permeability may be linked to sudden fetal death in the last trimester.

Case Report

A 32-year-old female presented for clinical evaluation five years after being diagnosed with rheumatoid arthritis and after one pregnancy that resulted in unexplained fetal death in the third trimester, and another pregnancy manifested by impending death based on cessation of fetal movement and fetal acidosis (but saved by emergency cesarean section). The patient was symptom-free prior to her first pregnancy but suffered from sore and stiff joints postpartum. She sought rheumatologic treatment and tested positive for rheumatoid factor. She delivered following spontaneous labor at 37 weeks. She was diagnosed with rheumatoid arthritis four months after her first pregnancy based on blood tests and symptoms which were indicative of rheumatoid arthritis. Her rheumatoid arthritis caused her to have severe unbearable pain. In addition to her arthritic symptoms and severe pain she also suffered from severe fatigue. The patient had failed to respond to standard pharmacologic therapy for the arthritis and presented with symptoms of severe intense pain and fatigue which was debilitating.

About a year after delivery the patient conceived but suffered an unexplained stillbirth at 31 weeks. Just two weeks prior everything had looked perfect on ultrasound. Pathological evaluation found no fetal abnormalities. The placenta weighed 312 grams. There was a 3-vessel umbilical cord. The villi were cellular with abundant lymphocytes; plasma cells were not prominent. No viral inclusions were identified. The membranes were unremarkable. The final diagnosis was chorionic villitis. Though there was no evidence of thrombosis of vessels on pathological evaluation of the placenta, a full coagulation profile of the mother was performed. Factor V Leiden mutation was not detected, protein C activity was normal at 129% (nl 70-140%) as was protein C antigen at 104% (nl 69-140%). Though protein S activity was somewhat low at 42% (nl 65-140%) protein C activity was 124% (nl 70-140%) and antigen was 104 (nl 65-140%). Anti-thrombin III was 101% (nl 75-125%) and the test for methylenetetrahydrofolate reductase mutation was negative and homocysteine was normal at 6.5 μmol/l. Tests for infectious etiologies including herpes simplex virus 1 and 2, parvovirus B19, cytomegalovirus, and toxoplasmosis were negative.

Three years after her first delivery the woman conceived again. During this pregnancy she noticed an improvement in her arthritic symptoms. She was under the careful vigilance of perinatologists. She had been treated with supplemental vaginal progesterone suppositories during the first trimester. An ultrasound at 30.5 weeks was perfectly normal. At 31 weeks the woman did not feel any fetal movement. Despite a normal heart beat and heart rate no fetal movement was detected. A decision was made to perform an emergency cesarean section. Though there was marked fetal acidosis the baby girl responded quickly once outside the womb. The baby was discharged five weeks after delivery perfectly healthy and there were no physical or mental problems at 29 months.

The severe debilitating arthritis in the hands, elbows and knees returned shortly after delivery. The patient was treated with standard treatment for rheumatoid arthritis but failed to respond to NSAIDS as well as treatment with methotrexate and prednisone. She was next treated with adalimumab, a tumor necrosis factor alpha monoclonal antibody and showed an initial response, but this treatment ultimately did not provide long-term relief and was ineffective after a year.

The woman presented for evaluation of an alternative treatment regimen to the standard rheumatologic therapies which had previously failed. Sympathomimetic amine therapy has been successful in treating severe unexplained, pelvic and chest pain, as well as joint pain and chronic fatigue in patients diagnosed with idiopathic orthostatic cyclic edema [7-9]. The woman sought help from a reproductive endocrinologist more for hope in finding an endocrinological cause of her chronic fatigue. At evaluation the patient was currently on naproxen, an NSAID, and prednisone, 10 mg/day. This therapy was not providing the relief needed to carry out everyday activities.

A diagnosis of idiopathic orthostatic cyclic edema was considered and she was asked to perform a water load test. This test is performed by drinking 1500 ml of water in 30 minutes, voiding, then measuring the amount of urine excreted over the next four hours (the first day supine and the second day completely erect). Most women with idiopathic edema will excrete $\geq$ 1200 ml supine but $<$ 1200 ml erect [10, 11]. This woman excreted 1450 ml supine but only 1070 ml erect.

The patient was treated with sustained release dextroamphetamine sulfate 10 mg capsules daily [7, 10, 11]. Shortly after starting the therapy she noticed a decrease in her joint pain flare-ups and marked improvement of her fatigue. Six months after starting this therapy the patient noticed an improvement in her quality of life and ability to carry out activities without the fatigue and soreness she had previously experienced.

Discussion

Sympathomimetic amine therapy has been the main treatment of idiopathic orthostatic edema for over 50 years [12]. Dextroamphetamine sulfate has been effective in treating recalcitrant pain syndrome including gastrointestinal and pelvic pain syndrome [8, 9, 13, 14]. In the case of idiopathic edema sympathomimetic amines are believed to function by stabilizing capillary membranes and thus negate the increased capillary permeability, especially in the upright posture [7]. In many cases this increase in capillary permeability can lead to toxic and irritating substances leaking and being absorbed into the surrounding tissues [9, 15]. This toxin leakage with increased capillary permeability has been hypothesized to be associated with cases of interstitial cystitis, unexplained pelvic pain, and urticaria which were responsive to sympathomimetic amine therapy [9, 14, 15]. Edema-associated etiologies treated successfully with sympathomimetic amines include esophageal pain, gastroparesis, vasomotor flushing, chronic fatigue syndrome, unexplained weight gain, fibromyalgia, dyslexia, premenstrual syndrome and unexplained pelvic pain [8-9, 11, 13, 14, 16]. Some of these symptoms may be related to the effects of water retention per se whereas there is also the possibility that the symptoms are related to the increased vascular permeability and would be present even in the absence of overt edema.

In this case study the patient suffered from severe arthritic pain which was recalcitrant to standard treatment

options for rheumatoid arthritis. Based on the previous studies of dextroamphetamine use in cases of severe joint pain, chronic fatigue syndrome, and unexplained pain, it was used as an alternative therapy for this patient who had been unresponsive to previous treatment attempts. The inflammatory process itself involves the release of cytokines which promote increased capillary permeability to facilitate the recruitment of inflammatory mediators [1]. It is possible that the increased capillary permeability associated with inflammation can be compared to the increased capillary permeability seen in patients with idiopathic edema who are successfully treated with sympathomimetic amine therapy and was the reason for trying sympathomimetic amines in this patient. It is not clear in this woman whether the idiopathic edema exacerbated joint pain from rheumatoid arthritis or whether her joint pain was never related to the rheumatoid arthritis, i.e., she has positive rheumatoid factor but without idiopathic edema her pain would be non-existant.

Sympathomimetic amines are believed to function in these patients by stabilizing the capillary membranes and decreasing permeability [7, 10-11]. In this patient the combination of increased capillary permability around the joints due to the inflammatory process as well as the build up of toxins associated with her pain such as nitric oxide, inflammatory cytokines, and prostaglandins were possible targets of the sympathomimetic amine therapy.

One cannot necessarily conclude that there was any connection between the recalcitrant arthritis that only responded to sympathomimetic amine therapy and the mysterious villitis that was probably responsible for her third trimester fetal demise and possibly was also responsible for the near fetal loss of her third pregnancy. However, it does seem too coincidental to have two occult problems in the same woman. She and her husband indicated that they were interested in a third child but were considering using a gestational carrier. We suggested the possibility that she could be treated with sympathomimetic amines throughout the entire pregnancy. The couple are considering the option. If the therapy fails then the hypothesis of increased vascular permeability as a cause of stillbirth would be less tenable. However, a favorable outcome would not necessarily prove that the good outcome was not merely fortuitous. Nevertheless a favorable outcome with treatment with dextroamphetamine sulfate could give some credence to trying sympathomimetic amines for other cases of unexplained fetal demise in the third trimester especially if the mother has an abnormal water load test.

References

[1] Feldmann M., Brennan-Fionula M., Maini-Ravinder N.: "Role of cytokines in rheumatoid arthritis". *Annual Review of Immunology*, 1996, *14,* 397.

[2] Panayi G.S., Lanchbury J.S., Kingsley G.H.: "The importance of the T cell in initiating and maintaining the chronic synovitis of rheumatoid arthritis". *Arth. Rheumat.,* 1992, *35*, 729.

[3] Check J.H., Ostrzenski A., Klimek R.: "Expression of an immunomodulatory protein known as progesterone induced blocking factor (PIBF) does not correlate with first trimester spontaneous abortions in progesterone supplemented women". *Am. J. Reprod. Immunol.,* 1997, 37, 330.

[4] Szekeres-Bartho J., Barakony A., Polgar B., Par G., Faust Z., Palkovics T. *et al.*: "The role of gamma/delta T cells in progesterone-mediated immunomodulation during pregnancy: a review". *Am. J. Reprod. Immunol.*, 1999, *42,* 44.

[5] Doria A., Iaccarino L., Arienti S., Ghirardello A., Zampieri S., Rampudda M.E., Cutolo M., Tincani A., Todesco S.: "TH2 immune deviation induced by pregnancy: the two faces of autoimmune rheumatic diseases". *Reprod. Toxicol. Links,* 2006, *22,* 234.

[6] Hammoudeh M.: "Recurrent postpartum episodic rheumatoid arthritis". *J. Clin. Rheumatol.*, 2006, *12,* 196.

[7] Streeten D.H.P.: "Idiopathic edema: pathogenesis, clinical features and treatment". *Metabolism*, 1978, *27,* 353.

[8] Leskowitz S.C., Shanis B.S., Check J.H.: "Resolution of atypical chest pain during treatment for idiopathic orthostatic edema". *Am. J. Gastroenterol.,* 1990, *85,* 621.

[9] Check J.H., Katsoff B., Citerone T., Bonnes E.: "A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin: case reports". *Clin. Exp. Obstet. Gynecol.*, 2005, *32,* 247.

[10] Streeten D.H.P.: "Understanding and treating idiopathic edema". *Consultant,* 1980, 82.

[11] Check J.H., Shanis B.S., Shapse D., Adelson H.G.: "A randomized comparison of the effect of two diuretics, a converting enzyme inhibitor, and a sympathomimetic amine on weight loss in diet-refractory patients". *Endoc. Prac.*, 1995, *1*, 323.

[12] Thorn G.W.: "Approach to the patient with idiopathic edema or periodic swelling". *JAMA*, 1968, *206,* 333.

[13] Boimel P.J., Check J.H., Katsoff D.: "Sympthomimetic amine therapy may improve refractory gastroparesis similar to its effect on chronic pelvic pain case study". *Clin. Exp. Obstet. Gynecol.*, 2007, *34*, 185.

[14] Check J.H., Wilson C.: "Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines – case report". *Clin. Exp. Obstet. Gynecol.*, 2007, *34*, 55.

[15] Check J.H., Gentlesk M.J., Falanga V.: "Sympathomimetic amines in the treatment of chronic urticaria: Two case reports". *CUTIS*, 1984, *34,* 388.

[16] Check J.H., Katsoff D., Kaplan H.: "Idiopathic orthostatic cyclic edema as a unique etiology for vasomotor flushing in a normal estrogenic woman with normal day 3 follicle stimulating hormone – case report". *Clin. Exp. Obstet. Gynecol.* (in press).

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