Progesterone as a cause of eosinophilic pneumonia after *in vitro* fertilization

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**ABSTRACT**

Intramuscular progesterone has been reported to be infrequently associated with acute eosinophilic pneumonia in patients who have recently undergone *in vitro* fertilization. A 27-year-old female at 5 weeks gestation after *in vitro* fertilization presented with cough, fever, dyspnea, bilateral infiltrates, and eosinophilia. All infectious, neoplastic, and autoimmune evaluations were negative. She gradually improved with supportive care. This case demonstrates that progesterone in sesame seed oil may be an inciting agent for eosinophilic pneumonia and that removal of this agent may be sufficient for recovery in mild cases.

**ARTICLE HISTORY**

Received 29 July 2017
Accepted 9 November 2017

**KEYWORDS**

Eosinophilic pneumonia; *in vitro* fertilization; progesterone; sesame seed oil; eosinophilia

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1. **Introduction**

Acute eosinophilic pneumonia may commonly be confused with atypical pneumonia or acute respiratory distress syndrome (ARDS). It is characterized by hypoxemia, bilateral patchy infiltrates, and bronch/oalveolar lavage with > 25% eosinophils. While frequently idiopathic, it has been associated with changes in smoking habits and multiple medications. Intramuscular progesterone is a rarely reported cause in patients undergoing *in vitro* fertilization. Typically, management involves corticosteroids; however, we present a case of a woman who improved with only withdrawal of the offending medication and without corticosteroids.

2. **Case**

A 27-year-old G₁P₀ female at 5 weeks gestation presented to an urgent care center with 3 days of post nasal drip, nonproductive cough, low grade temperatures up to 100°F, but on the day of presentation had worsening cough, posttussive emesis, dyspnea, and chest pain. On initial presentation oxygen saturation was 87% on room air and she was requiring 3 LPM of oxygen through nasal cannula. Her initial vital signs were as follows: temperature 98.4°F, blood pressure 119/67 mmHg, pulse 100 beats per minute, respiratory rate 18 breaths per minute, and physical exam was significant for diffuse bilateral crackles. She had no edema.

Chest radiograph demonstrated bilateral patchy opacities (Figure 1). She had leukocytosis of 26.59 × 10³/µL, neutrophil predominant 15.47 × 10³/µL, but also notable for significant eosinophilia with a count of 7.01 × 10³/µL. These were all new findings as compared to lab work performed 8 months prior. Prolactin was 43.08 ng/mL. She was admitted and was started on ceftriaxone and azithromycin for probable community-acquired pneumonia (CAP).

Of note, she had recently undergone *in vitro* fertilization with frozen embryo transfer 3 weeks prior to presentation. She was given progesterone support starting 1 week prior to implantation with daily intramuscular injections. The plan had been to continue for the next 12 weeks, but this was held on admission. She was a lifetime nonsmoker. She had traveled to South Carolina about 6 months ago, but otherwise had no recent travel and no international travel. She had had a dog for many years, which was healthy. There were no recent changes to her diet or environment. Her review of systems was otherwise negative.

By day 2 of admission, her oxygen requirements had decreased to 1 LPM and she was feeling significantly better. However, she had persistent eosinophilia, up to 9.59 × 10³/µL on day 3, leading to consultation of Infectious Disease, Pulmonology, and Hematology/Oncology.

Infectious workup was all negative, including HIV antibody and antigen screen, *Cryptococcus* antigen, urinary *Histoplasma* antigen, stool ova and parasite exam, *Blastomyces dermatitidis* antibody, *Toxoplasma* antibodies, *Strongyloides* antibody, *Toxocara* antibody, *Ascaris* IgE, *Micropolyspora* antibody, *Thermoactinomyces* vulgaris antibody, fungitell, and stool for *Clostridium difficile* by PCR.
Autoimmune and neoplastic workup was also unremarkable, including ANA, ANCA, ESR, respiratory allergy IgE panel, tryptase, and JAK2 V617F mutation. She had a normal vitamin B12 and immunoglobulin levels including IgE. She had a normal peripheral blood flow cytometry.

She underwent a bone marrow biopsy on day 7 of admission. This demonstrated hypercellular bone marrow for age with trilineage hematopoiesis and marked increase in eosinophils with normal flow cytometry and chromosomal analysis.

She completed treatment for CAP, oxygen was weaned to room air, and she was feeling well. Because of her marked clinical improvement, bronchoscopy was not performed. With no oxygen requirement, she was discharged home. Obstetrics switched her progesterone to a preparation without sesame seed oil on discharge. Repeat complete blood cell count 3 weeks after initial presentation demonstrated decreasing eosinophil count, with normalization by 4 months. Her pregnancy with dichorionic diamniotic twins progressed without significant complications.

3. Discussion

Eosinophilic pneumonia usually presents as an acute onset of dyspnea, fever, cough, and pleuritic chest pain. It is frequently misdiagnosed as infectious pneumonia or ARDS due to the usually normal eosinophil count. Although it may remain normal, when it does rise it typically exceeds normal values within the first few days. Chest radiographs reveal bilateral mixed alveolar and interstitial opacities, and CT scans frequently demonstrate bilateral ground glass opacities, septal thickening, pleural effusions, and airspace consolidation. Diagnosis is confirmed with bronchoalveolar lavage showing negative cultures and a finding of >25% eosinophils [1].

Due to her current pregnancy, diagnostic certainty was difficulty in this patient, as she was unable to undergo CT scan of the chest. Because she was clinically improving, the risks of bronchoscopy were thought to outweigh any potential benefits of diagnostic certainty.

The exact etiology of eosinophilic pneumonia is often idiopathic; however, there are many known precipitants. Changes in smoking patterns are among the most common causes [1], but there are also many medications which can precipitate eosinophilic pneumonia [2]. While not a common cause, intramuscular progesterone has been described in case reports [3–8].

Intramuscular progesterone is commonly used for luteal phase support in patients undergoing in vitro fertilization [3]. In a majority of the available case reports, patients developed eosinophilic pneumonia after 2–4 weeks of intramuscular progesterone therapy. Additionally, the progesterone preparations for all used sesame seed oil as an excipient [3–7]. A prior case report demonstrated initial improvement in a patient’s symptoms with discontinuation of intramuscular progesterone, but return of symptoms with reintroduction [6]. In the absence of elevated IgE, these cases have been postulated to be secondary to a delayed-type hypersensitivity reaction to either sesame seed oil itself or proteins contaminating the oil [3,5,8]. In one case report, intradermal injections of progesterone produced significant areas of induration, supporting this hypothesis [5].

The management of eosinophilic pneumonia involves removal of the inciting agent and corticosteroids. Typical dosing is prednisone 30 mg daily or intravenous methylprednisolone 1–2 mg/kg/day for respiratory failure [1]. Our patient had resolution of hypoxemia and significant improvement in symptoms with only removal of the progesterone and without corticosteroids. In pregnant patients who have undergone in vitro fertilization, transitioning to a progesterone preparation with peanut oil as an excipient or an intravaginal progesterone is a viable alternative [5,6].

4. Conclusions

Eosinophilic pneumonia should remain on the differential diagnosis for pneumonia and ARDS, regardless of serum eosinophil count. In patients who have recently undergone in vitro fertilization, intramuscular progesterone in sesame seed oil administered for luteal phase support may incite a delayed hypersensitivity reaction causing eosinophilic pneumonia. Clinicians should keep in mind that, like in this
case, the inciting agent may take several weeks to cause an immunologic response. In less severe cases of eosinophilic pneumonia, merely removing this agent may be enough to lead to clinical recovery.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
No funding was obtained or used for this case report.

Geolocation information
40.7029° N, 89.5920° W

References
[1] Cottin V. Eosinophilic lung diseases. Clin Chest Med. 2016;37:535–556.

[2] Pneumotox [Internet]. Dijon (France): Department of Pulmonary Medicine and Intensive Care University Hospital; 2013 [cited 2017 Jul 24]. Available from: www.pneumotox.com

[3] Khan A, Jariwala S, Lieman H, et al. Acute eosinophilic pneumonia with intramuscular progesterone after in vitro fertilization. Fertil Steril. 2008;90(4):1200e3–1200e6.

[4] Dagar G, Uysal Biggs N, Tomic R, et al. Eosinophilic pneumonia caused by IM progesterone treatment for in vitro fertilization. Chest. 2011;140(4_Meeting Abstracts):154A.

[5] Boukaert Y, Robert F, Englert Y, et al. Acute eosinophilic pneumonia associated with intramuscular administration of progesterone as luteal phase support after IVF: case report. Hum Reprod. 2004;19(8):1806–1810.

[6] Phy J, Weiss W, Weiler C, et al. Hypersensitivity to progesterone-in-oil after in vitro fertilization and embryo transfer. Fertil Steril. 2003;80(5):1272–1275.

[7] Veysman B, Vlahos I, Oshva L. Pneumonitis and eosinophilia after in vitro fertilization treatment. Ann Emerg Med. 2006;47(5):472–475.

[8] Richards C, Hsu D, Weinstock T, et al. Eosinophils: an unexpected delivery. Ann Am Thorac Soc. 2013;10 (4):390–392.