Acute eosinophilic pneumonia associated with intramuscular administration of progesterone as luteal phase support after IVF: Case report

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We report two cases of acute eosinophilic pneumonia induced by i.m. administration of progesterone used as luteal phase support after IVF. For both patients, the symptoms began 3 weeks after the first injection of progesterone. Both patients were in respiratory distress, and one of them required ventilatory assistance for a week, with 5 days in the intensive care unit. Symptoms improved as the i.m. form was shifted to a vaginal form of progesterone together with the administration of corticosteroids. Sesame oil (used as excipient) and benzyl alcohol (used as preservative) could both be incriminated in the development of the hypersensitivity reaction. The need for luteal phase support is clearly established in IVF cycles with GnRH agonist protocols, and progesterone is the generally recommended compound. However, there is no definitive consensus regarding the optimal route of administration of progesterone. These two cases of acute drug-induced disease show that the use of i.m. progesterone can be associated with a severe morbidity in otherwise healthy young patients. This is an additional argument to advocate the use of vaginal progesterone as luteal support in IVF.

Key words: benzyl alcohol/eosinophilic pneumonia/IVF/progesterone/sesame oil

Introduction

Eosinophilic pneumonia is a syndrome characterized by non-specific pulmonary symptoms varying from mild to severe, life-threatening, respiratory failure. The diagnosis is usually suggested by peripheral alveolar opacities at the chest X-ray, with alveolar and usually peripheral blood eosinophilia (Cordier, 1998).

The diagnosis can be suspected upon history, but the delay after drug intake is variable. The diagnosis is confirmed by the improvement of the symptoms following withdrawal of the suspected medication. In severe cases, corticosteroid treatment is indicated.

We report two cases of acute eosinophilic pneumonia following i.m. administration of progesterone in sesame oil (excipient) and benzyl alcohol (preservative) after IVF. Drug-induced eosinophilic pneumonia related to luteal phase support in IVF has never been reported before (see www.pneumotox.com).

Case reports

Patient 1

A 39 year old Congolese woman was admitted in the emergency room with productive cough, dyspnoea, asthenia and anorexia. Because of mechanical infertility, she had been treated by IVF. Ovarian stimulation for IVF had been carried out by a desensitizing protocol using a short-acting GnRH agonist preparation together with urinary gonadotrophins. Three embryos had been transferred 3 weeks before admission. The pregnancy test was positive 2 weeks later. As luteal phase support, she received from the transfer day a daily i.m. injection of 100 mg of progesterone in sesame oil as an excipient and benzyl alcohol as a preservative (Sterop, Belgium).

The only relevant disease in her past medical history was malaria. In the context of her secondary infertility evaluation, the patient had undergone a laparoscopy 2 years before, which revealed adhesions between the right Fallopian tube and the uterus. A first IVF attempt had been cancelled because of premature ovulation. She had no known allergy and was a non-smoker. She had been living in Belgium for 5 years and had not left Europe during this time. She had three children all in good health.

On admission, the patient was in respiratory distress with a respiratory rate of 30 breaths/min and a regular heart rate at 100 beats/min. Examination revealed bilateral basal crackles and diminished breathing sounds.

The chest X-ray on admission showed interstitial infiltrates predominating in the periphery of both lungs (Figure 1).
Arterial blood gas analysis at room air indicated a PaO₂ of 66 mmHg and an oxygen saturation of 94%. Laboratory findings were as follows: white blood count: 29.5 £ 10⁹/mm³ with 47% of eosinophils representing 12.2 £ 10³ cells/mm³; C-reactive protein 13 mg/dl (normal, 0.5 mg/dl). Cytological analysis of bronchoalveolar lavage (BAL) fluid performed in the right lower lobe the day of admission identified 8 £ 10⁶ nucleated cells/ml with 69% eosinophils, 20% macrophages, 5% lymphocytes, 4% basophils and 2% neutrophils. Cultures of BAL fluid were negative for viruses, fungi, parasites and bacteria. Haemocultures were also negative. Serological studies for parasites showed only antibodies for *Plasmodium falciparum*, corresponding to a known past disease. HIV serology was negative. Cultures of sputum, faeces and urine did not show pathogenic organisms.

As the patient was treated with i.m. injections of progesterone, the hypothesis of a hypersensitivity reaction against one of the components of the progesterone ampoules was tested using an intradermal test and a lymphoblastic transforming test (LTT). The intradermal test was performed by injecting directly into the skin 0.05 ml of different dilutions (1/10, 1/100 and 1/1000) of the whole preparation (progesterone 50 mg, benzylic alcohol 100 mg, sesame oil 2 ml). Saline 0.9% was used as negative control. As the three dilutions induced significant induration and erythema, the test was considered positive. Moreover, a lymphoblastic transforming test with the whole preparation was positive. Total immunoglobulin E level was normal. The research for specific IgE against sesame using the radio-allergo-sorbent test (RAST) was negative. The autoimmune screening demonstrated low levels (1/16 dilution) of antineutrophil cytoplasm antibodies (ANCA).

The first treatment she received in the emergency room was oxygen and amoxicillin–clavulanic acid. As the different cultures were negative, the antibiotics were stopped and a presumptive diagnosis of eosinophilic pneumonia was made. Because of the pregnancy, progesterone administration was continued but the i.m. form was shifted to an intravaginal form, free of sesame oil or benzylic alcohol (Utrogestan Belgium).

The patient was treated with i.v. corticosteroids (120 mg of methylprednisolone per day) during 3 days followed by 64 mg of oral methylprednisolone with decreasing doses during 3 weeks.

The clinical evolution was quickly favourable, but 5 days after admission the blood eosinophil count in remained very high at ~15 000/mm³. A bone marrow aspirate was then performed and showed 41% of mature eosinophils and a normal population of lymphocytes. Peripheral lymphocyte profile was normal, excluding a myeloproliferative disease.

Pulmonary function tests (PFT) on day 5 revealed a pure restrictive defect, with a total lung capacity of 3.05 l (59.8% of predicted), a vital capacity (VC) of 2.12 l (60.9% of predicted) and a reduced CO diffusion capacity (TLCO) (60.3% of predicted). On day 9, PFT showed nearly normal volumes, but the TLCO remained low (66.9% of predicted). A chest X-ray on day 10 showed a clear regression of the bilateral interstitial infiltrates (Figure 2).

The absolute number of eosinophils decreased after 9 days and the patient was discharged with oral methylprednisolone and vaginal progesterone tablets.

Three months after discharge, a blood analysis showed a normal count of white blood cells (6.3 £ 10⁹/mm³) with 3.5% eosinophils. The patient was at that time in the fourth month of her pregnancy. The pregnancy progressed uneventfully and the patient delivered a healthy girl at term.

**Patient 2**

A 38 year old woman was admitted because of fever, cough and dyspnoea. The patient had undergone a first IVF treatment because of her husband’s tetraplegia-associated anejaeculation. Ovarian stimulation for IVF had been performed by a desensitizing protocol using a short-acting GnRH agonist preparation together with urinary gonadotrophins. Three embryos obtained by ICSI following surgical sperm retrieval by testicular sperm extraction had been transferred 3 weeks before admission. A pregnancy test was positive 2 weeks later. As luteal support, the patient received daily i.m. injections of 100 mg of progesterone in sesame oil and benzylic alcohol. From the embryo transfer onwards, the patient was also treated with daily s.c. injections of 40 mg of enoxaparin because of protein S deficiency.

The patient had been pregnant twice in a previous relationship (one spontaneous abortion and one delivery at term). She was a non-smoker and had no known allergy. Cough and dyspnoea had started 2 weeks after the embryo transfer. During the third week, the patient developed fever, cough and dyspnoea. The chest X-ray on admission showed bilateral infiltrates, predominantly located in the periphery of the lungs.

**Figure 1.** Patient 1. Chest X-ray on admission (day 1) shows bilateral infiltrates, predominantly located in the periphery of the lungs.
worsening of her respiratory distress and prurit on the injection site of progesterone.

On physical examination, the temperature was 38.8°C, the heart rate regular at 120/min and the respiratory rate 36/min. Pulmonary examination revealed basal crackles. Cardiac, abdominal and neurological examination were normal. The chest X-ray showed bilateral interstitial infiltrates. Arterial blood gas analysis at room air indicated a PaO2 of 57 mmHg. Laboratory findings showed a white blood cell count of 22.5\times10^3/mm^3, with 4.9% of eosinophils representing 1105 cells/mm^3. The C-reactive protein was observed at 18 mg/dl (normal, 0.5 mg/dl). Her total IgE level was normal. Pulmonary embolism was excluded by a ventilation–perfusion isotopic lung scan and deep vein thrombosis by Doppler ultrasound. Echocardiography was normal. BAL could not be performed because of severe hypoxaemia. Cultures of sputum, faeces and urine and haemocultures did not show pathogenic organisms. The autoimmune screening (ANCA, antinuclear antibodies) and viral serologies were normal (influenza, para-influenza, chlamydia pneumoniae, mycoplasma, adenovirus and legionella).

The first treatment she received in the emergency room was oxygen, amoxicillin–clavulanic acid and clarithromycin. Antibiotics were stopped as cultures were negative for bacteria. As her ventilation conditions worsened, the patient was transferred into the intensive care unit where she was administered a continuous positive airway pressure (CPAP) with a FiO2 of 80% and a positive end expiratory pressure (PEEP) at 8 cm of water to maintain a PaO2 at \(\sim 50\) mmHg. On the third day of hospitalization, erythema appeared on her left buttock (site of progesterone injection). A drug-induced eosinophilic pneumonia was suspected. The i.m. form of progesterone was shifted to an intravaginal form. Corticosteroids were added (methylprednisolone 2 mg/kg) during 1 day followed by decreasing doses during 4 weeks.

Respiratory function rapidly improved, the absolute number of eosinophils decreased, the chest X-ray showed a regression of the infiltrates and the patient was discharged with oral methylprednisolone.

The test for specific IgE against sesame using the RAST was negative, as was the LTT against sesame oil and against progesterone. The pregnancy progressed uneventfully and the patient delivered a healthy girl at term.

**Discussion**

Luteal phase support has become a routine procedure during IVF treatments. The addition of GnRH agonists to the IVF treatments has been associated with an impairment of the corpus luteum and with a relative progesterone deficiency (Smitz et al., 1988). Luteal phase supplementation has mainly consisted of progesterone or hCG. Both agents have been shown to significantly improve fertility outcomes in IVF cycles using a GnRH agonist (Soliman et al., 1994). Because hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS; McClure et al., 1992), progesterone has become the agent of choice for luteal supplementation. Progesterone can be administered orally, i.m., or vaginally (Tavaniotou et al., 2000; Ludwig and Diedrich, 2001). Oral progesterone is subjected to first-pass hepatic metabolism leading to a low bioavailability, and is associated with a large number of side-effects such as drowsiness, flushing and nausea. Moreover, in a meta-analysis of randomized trials, oral progesterone has been shown to be less effective than vaginal progesterone or hCG regarding implantation rates (Pritts et al., 2002). I.m. injections of progesterone can be painful and may lead to marked inflammation and even to sterile abscess formation at the injection site (Tavaniotou et al., 2000). Vaginal application of progesterone has been reported to cause local irritation and vaginal discharge (Kimzey et al., 1991). The comparison of i.m. and vaginal progesterone administration regarding reproductive benefits is still a matter of controversy (Penzias, 2002). Endometrial progesterone levels are higher after vaginal than after i.m. administration of progesterone, despite higher serum progesterone levels after i.m. administration (Miles et al., 1994; Cicinelli et al., 2000). Supplementation with vaginal progesterone is postulated to be subjected to first uterine pass effect, leading to higher uterine tissue levels and better endometrium synchronization (Bourgain et al., 1994). However, in a recent meta-analysis of randomized trials, the i.m route conferred higher clinical pregnancy and delivery rates than

**Figure 2.** Patient 1. Chest X-ray on day 10 shows a dramatic regression of the pulmonary infiltrates after corticotherapy and shifting the progesterone from an i.m. form (with sesame oil as excipient and benzylic alcohol as preservative) to vaginal tablets (with peanut oil as vehicle).
the vaginal route, whereas no differences could be demonstrated between both preparations regarding implantation rates, ongoing pregnancy rates and miscarriages (Pritts and Atwood, 2002).

To the best of our knowledge, we report for the first time in two patients, a severe systemic allergic reaction to i.m. administration of progesterone. For both patients, it was the first exposure to luteal phase support. The patients had no known allergies and the respiratory symptoms developed around 3 weeks after starting the i.m. injections of progesterone.

Acute and chronic eosinophilic pneumonia may be idiopathic or be related to various causes such as parasitic infections (Löffler syndrome) and drug-induced toxicity (Allen and Davis, 1994). Less frequent causes of pulmonary eosinophilia are the Churg–Strauss syndrome (a vasculitis usually associated with antineutrophil cytoplasm antibodies) and allergic bronchopulmonary aspergillosis. The clinical and radiological patterns of these diseases are, however, different from those of acute eosinophilic pneumonia.

Eosinophilic pneumonia of parasitic origin should be excluded by stool smears and serological methods (Toxocara, Fasciola, Trichinella, Strongyloides etc.). Many medications, including common antibiotics, are liable to cause eosinophilic pneumonia (an updated list is available on the pneumotox website: www.pneumotox.com). The disease can also be induced by inhalation of illicit drugs (cocaïne, crack).

Specific allergic factors associated with the disease can be diagnosed using skin tests and lymphoblastic transforming tests (LTT). Skin tests assess immediate type hypersensitivity and LLT tests evaluate the proliferation and activation of lymphocytes put in contact with the allergen. The intradermal test and the lymphoblastic transforming tests to the solution from the progesterone ampoule were both positive for the first patient when the whole preparation was tested. The research for specific IgE against sesame using the radioallergo-sorbent was negative. The fact that the two patients developed similar symptoms using the same preparation of i.m. progesterone and that they both recovered when shifting to a vaginal form (with peanut oil as excipient) is highly suggestive of an allergic reaction to a constituent of the preparation used rather than to progesterone itself. Based on the tests performed, we cannot draw firm conclusions about the nature of the allergen which can be either sesame oil or benzyl alcohol. Hypersensitivity reactions to sesame oil and to benzyl alcohol have been previously reported but have never been presented as eosinophilic pneumonia (Grant et al., 1982; Shmunes et al., 1984; Kanny et al., 1996).

Other i.m. preparations of progesterone are available at least in some countries, including the USA, that use other vehicles such as peanut oil. Vaginal preparations usually also use peanut oil as excipient. Hypersensitivity reactions to peanut oil have been described, mainly in relation to food allergy and reactions to meals in subjects allergic to peanuts (O’B Hourihane et al., 1997). To the best of our knowledge, peanut oil has not been implicated in allergic reactions as part of a progesterone preparation for luteal support.

Nevertheless, acute eosinophilic pneumonia can be induced by i.m. administration of progesterone. The condition can be life-threatening if the diagnosis is not rapidly suspected. For the second patient, respiratory support in the intensive care unit was required for 1 week. Clinicians should be aware that the condition can develop after several weeks of exposure to the allergen.

The need for luteal phase support is clearly established in IVF cycles with GnRH agonist protocols, and progesterone is the generally recommended compound, as it is associated with a lower incidence of ovarian hyperstimulation syndrome. However, there is no definitive consensus regarding the optimal route of administration of progesterone nor concerning the duration of the treatment. Recent studies have indeed suggested that luteal phase support beyond the pregnancy test might not be needed (Tryde Schmidt et al., 2001). These two cases show that the use of i.m. progesterone can be associated with a severe morbidity in young, otherwise healthy, patients. The severity of the symptoms is an additional argument for the use of vaginal progesterone as luteal phase support in IVF.

References


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