

# Episcleritis as a possible complication of lymphocyte immunotherapy - case report

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## Summary

**Introduction:** Recurrent episcleritis is uncommon. Lymphocyte immunotherapy (LIT) is frequently useful in establishing successful pregnancies in women with previously failed in vitro fertilization (IVF) cycles. **Methods:** A woman with recurrent episcleritis and previous splenectomy was carefully questioned to see if there was any association with having had the LIT procedure. Methylprednisone 10 mg/day x 5 days was always given before embryo transfer because of assisted embryo hatching. **Results:** There was a tendency for the episodes to occur immediately after the LIT, especially four days after embryo transfer. However, they also occurred several times between IVF cycles before she ovulated. **Conclusions:** Since she had never had an episode of episcleritis before LIT and because she always developed the problem shortly after the procedure it seems that the procedure could have this potential side-effect. The possibility exists that LIT may not cause this problem in people with intact spleens. Possibly, the use of an immunosuppressive, e.g., methylprednisone exacerbates the problem.

**Key words:** Lymphocyte immunotherapy; Episcleritis, Corticosteroids; Splenectomy.

## Introduction

Lymphocyte immunotherapy (LIT) has been used to help reduce the risk of miscarriage in women with a history of recurrent miscarriage [1-9]. It has also been used to improve the chance of a successful pregnancy following in vitro fertilization-embryo transfer (IVF-ET) in women who have failed to achieve a successful pregnancy despite several previous embryo transfers [10-12].

Episcleritis is an inflammatory condition affecting the episcleral vessels of the eye. These vessels lie deep in the outermost conjunctiva and are superficial to the sclera. The presentation is an acutely red and mild painful eye, usually occurring in young adults. One or both eyes may be affected. In most cases a discrete segment of the usual white of the eye becomes intensely red. Less commonly the episcleritis is diffuse in character and much of the front of the eye becomes red.

Although the cause is usually unknown and not associated with systemic conditions, there is a small percentage of patients that will have rheumatoid arthritis or other collagen vascular diseases, such as systemic lupus, erythematosis, polyarteritis nodosa or Wegener's granulomatosis.

Lymphocyte immunotherapy has been demonstrated to be helpful in patients who have had recurrent failure to conceive, following in vitro fertilization-embryo transfer [10-12] and has also been helpful in inhibiting spontaneous miscarriage in women with recurrent spontaneous abortion and habitual aborters [1-9]. The theoretical mechanism may involve a shifting of thymic helper

(TH)1 to TH2 cytokines. The shift to TH2 cytokines inhibits the cellular immune reaction and causes a humeral immune reaction. The mechanism may be related to the fact that the white blood cell is 100 to 1,000 times more potent than the fetus as an allogeneic stimulus which is needed to induce de novo progesterone (P) receptors in gamma/delta T cells [13-16]. The interaction of high doses of P generated at the maternal-fetal interface reacts with the P receptor on the gamma/delta T cells leading to the expressing of the progesterone-induced blocking factor which suppresses natural killer cell function [13, 16-18].

## Case Report

The patient is at the present time 35 years old and has had infertility going back two and a half years. Overall, she has never had a delivery and has had three pregnancies, all of which were chemical, nothing that even got to ultrasound evidence of pregnancy. The cause of her infertility was premature luteinization but also failure to develop a homogeneous hyperechogenic pattern to her midluteal phase endometrium [19-21]. After many cycles of failure of correcting those entities, she decided to undergo IVF.

All told, she has had five cycles of IVF. The first IVF-ET she did not have lymphocyte immunotherapy (LIT). But she showed an allergic reaction to doxycycline as manifested by having to go to the emergency room with diarrhea, cramps, respiratory problems, etc. She was given methylprednisolone, 16 mg a day for five days in preparation for embryo hatching. However, she did not have an episode of episcleritis in that IVF cycle. She failed to conceive in that cycle.

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The second cycle with lower dose stimulation, she produced three mature follicles and two embryos and we thawed the three frozen embryos and thus she had five embryos transferred. Again, she took doxycycline and got sick so it then became obvious that there was a side-effect to the doxycycline. It was not clear before, and it was just thought that she had some kind of coincidental viral or bacterial illness. Nonetheless it seemed to be certain that it was an allergic reaction to the doxycycline. But again, no episcleritis, despite once again taking the methylprednisolone.

The third cycle, she had lymphocyte immunotherapy that preceded her next IVF cycle by three months. She did not develop episcleritis following the LIT procedure and she actually had no overt side-effects.

She started her fourth IVF cycle a month later. Four days after transfer, she developed episcleritis. The episcleritis lasted five days and was treated with steroid eye drops and also antibiotic eye drops. She had a chemical pregnancy.

We started IVF again. In the middle of that cycle she went to Mexico for LIT again, and had another immune procedure performed. Episcleritis developed again, less than a week after transfer. Again it took about five days to resolve and the treatment this time was just the steroids, without the antibiotics.

The episodes of episcleritis and conjunctivitis occurred again about three weeks after the LIT. In that cycle, she did not have IVF. The episcleritis was not associated with her ovulation as it occurred on day 7 of her cycle. It also occurred on day 19; she did not ovulate until day 23. Thus, it was not a progesterone-associated event, but may have still been related to the previous LIT.

Her next episode of episcleritis occurred 45 days from her previous LIT. That was also not associated with an IVF cycle or transfer. She had five more episodes after that without having IVF. She had one last episode of episcleritis four days after embryo transfer.

It should be noted that she had a fasting serum glucose, liver function studies, kidney function studies, rheumatoid factor, antinuclear antibody, Lyme's disease serum and nothing was found to be abnormal. Also, her TSH was normal as was her complete blood count. Past medical history revealed previous splenectomy related to an automobile injury.

## Discussion

Interestingly, these episodes of episcleritis never occurred before LIT and have only occurred since the patient had this procedure. Although they can occur without IVF, it is interesting that in the three times it occurred with IVF, it was always four days after embryo transfer. Whether taking the methylprednisone in preparation for the assisted embryo hatching had anything to do with it remains to be seen, or the possibility is that it could be coincidental. However, the ingestion of methylprednisone prior to LIT never led to these episodes of episcleritis.

It is not clear if this problem of episcleritis occurred subsequent to an LIT procedure. It just seems odd that when it did happen during an IVF cycle, it was always four days after transfer. The ophthalmologist has never really been aware of anybody getting this type of condition in such a recurrent fashion. The data does not strongly show an association between lymphocyte immunotherapy and episcleritis on a recurrent basis, but certainly it is consistent with this possibility. The conclusion from this anecdotal report is simply that when asked about what complications could possibly occur from lymphocyte immunotherapy that the treating physician should suggest the possibility that one could develop this problem of recurrent episcleritis-conjunctivitis. In fact, the condition may keep recurring even as long as six months after the LIT has been done.

Though in the IVF cycle antibiotics are also used, during the times that the patient had these episodes she was not having IVF, and she was not on antibiotics or steroids. Furthermore it did not happen in association with her luteal phase so it does not appear to be a progesterone-related event. Nonetheless it does seem odd that it happened several days after transfer when she underwent the IVF, which either could be coincidental or perhaps it does have something to do with the methylprednisolone being something that could actually precipitate it. However it is not the only mechanism to activate episcleritis since she had it in cycles when she did not take glucocorticosteroids. Further study of her case may shed some more light on this problem.

It is not clear what role her previous splenectomy played in these episodes. The possibility exists that LIT can precipitate episcleritis only in people with previous splenectomies.

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