Case Report

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Successful pregnancy after cyclophosphamide therapy for systemic lupus erythematosus: a case report

Tasneem Drie, MD[a,*], Mhd Imadaldin Alsamman, MD[b], Raghad Tarcha, MD[a], Ghina Haidar, MD[a], Maysoun Kudsi, PhD, MD[c]

Introduction and importance: The use of cyclophosphamide in women of childbearing age with severe systemic lupus erythematosus is normally indicated. However, cyclophosphamide is generally avoided during pregnancy due to the risk of teratogenicity, especially since its effect on fetal survival is poorly understood. This is a case report of a lupus patient exposed to cyclophosphamide during pregnancy.

Case presentation: A 35-year-old woman with a history of lupus presented to our outpatient clinic in the 12th week of pregnancy for her sixth routine cyclophosphamide bolus. The fetal echocardiogram result with the gynecology consultation was normal with the recommendation for a medical termination of pregnancy, which has been refused by the patient. Shared decision-making with the patient included a discussion of the maternal risks of continuation of pregnancy in the setting of worsening systemic function and the fetal risks of definitive treatment with cyclophosphamide for a lupus flare and the patient decided to proceed with the pregnancy. Treatment with immunosuppressants, including azathioprine was initiated replacing cyclophosphamide with close monitoring of her and the fetus every month.

Clinical discussion: The first trimester of pregnancy seems to be particularly susceptible to fetal malformations, although CPA effects on fetuses in later stages of pregnancy are also reported occasionally. Nonetheless, its repercussions on fetal survival remain poorly comprehended.

Conclusion: In conclusion, exposing pregnancy to cyclophosphamide could end with pregnancy loss. Based on our experience, the survival of the fetus is strongly in doubt when cyclophosphamide is required to treat lupus in the mother. However, in rare cases, it could be without complications.

Keywords: cyclophosphamide, successful pregnancy, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease, that affects all body organs, leading to damage to the system functions, increased morbidity, and mortality[1].

SLE itself does not increase the risk of infertility, active disease, advanced maternal age, renal insufficiency, and prior exposure to cyclophosphamide can contribute to difficulties conceiving. SLE patients can undergo assisted reproductive technologies as long as the disease is under good control. Pre-eclampsia and maternal morbidity are more common in severe patients, and poor pregnancy outcomes are increased[2].

Cyclophosphamide is an alkylating agent from the group of oxazophosphorines or nitrogen mustard compounds, used in the treatment of auto-inflammatory immune diseases such as vasculitis, scleroderma, SLE, and others[3,4].

SLE often affects females of reproductive age and cyclophosphamide, leading to premature ovarian insufficiency, and labeled category D for pregnancy is used as induction therapy for severe manifestations of lupus[5].

Cases of malformation have been described in newborns of mothers who received cyclophosphamide in the first months of pregnancy. Nonetheless, its repercussion on fetal survival remains poorly comprehended[6].

The risk of cyclophosphamide-related infertility is associated with both the cumulative dose and the age at which the drug is first administered, which is greatest for those younger than 30 years, and for those receiving six or fewer intravenous doses, including cumulative doses of fewer than 7 g[7,8].

Cryopreservation of either oocytes or embryos is an effective option for fertility preservation when cyclophosphamide must be used[9]. However, it necessitates ovarian stimulation, which may be impractical given the need to institute therapy promptly to prevent damage, as well as the risk of hyperstimulation in an already active sick patient[10,11].

[a]Rheumatology Department, Faculty of Medicine, Damascus University, [b]Surgery Department, Faculty of Medicine, Damascus University and [c]Damascus University, Syrian Arab Republic

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*Corresponding author. Address: Rheumatology Department, Faculty of Medicine, Damascus University, Damascus, Syria. Tel.:/fax: +963 948 958 318.
E-mail: samsomadrei@gmail.com (T. Drie).

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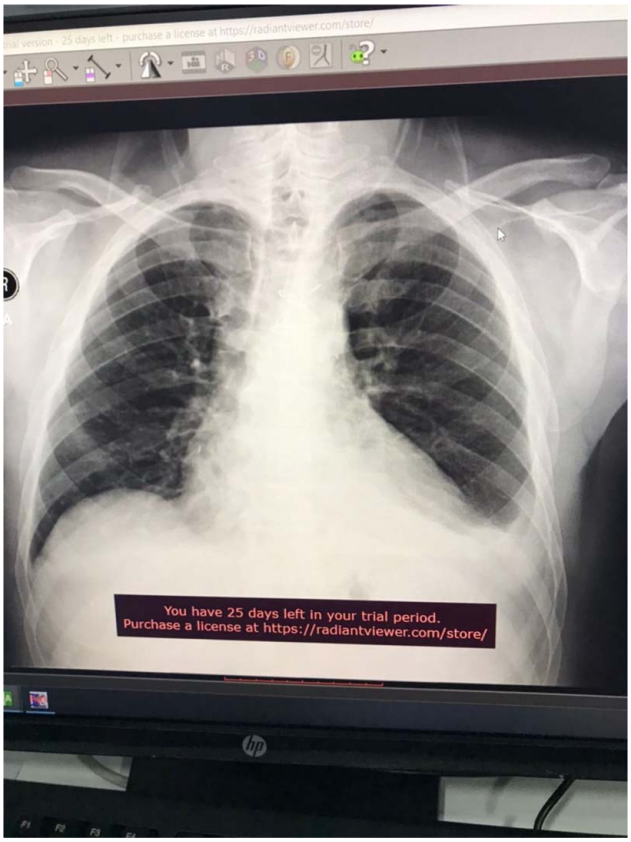


Figure 1. Shows bilateral effusion.

Case presentation

A 35-year-old married female with two healthy boys, admitted to our outpatient clinical, in May 2021, complaining of progressive edema of the lower extremities and dyspnea. She was diagnosed with SLE, according to the American College of Rheumatology/European League Against Rheumatism 2010[12] 3 years ago. She had a malar rash, oral aphthae, pancytopenia, and thrombosis in the retinal vessels, with moderate positive for antiphospholipid, positive and at 1/320, positive, and anti-DS DNA at 68, positive.

She was treated with pulse methylprednisolone for 3 days, then with prednisolone (1 mg\kg) with a taper to 5 mg till now, azathioprine (1 g\day), and 81 mg/day aspirin. Now, the prednisolone dose is 5 mg/day.

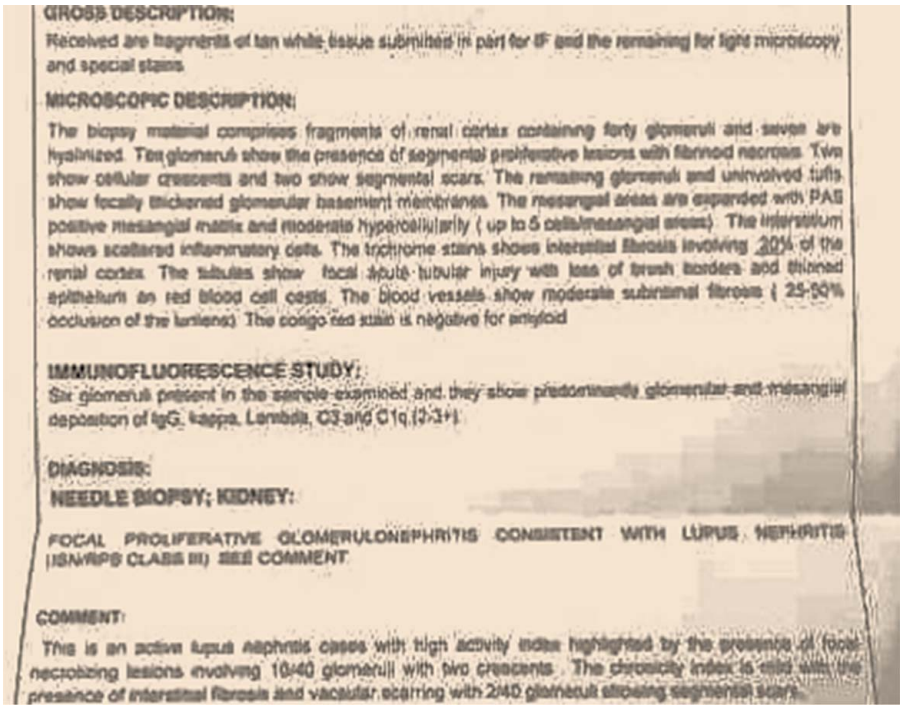
A physical examination showed that her heart rate was regular at 117 beats per minute, her respiratory rate was 20 breaths per minute, and her blood pressure was 110/70 mmHg. Edema of the lower extremities, II-degree extension, VI-degree depth, respiratory examination showed a lack of sound vibrations, deafness, and fainting of breathing sounds at the bases. The rest of the examination was normal.

Laboratory tests were:

white blood cells at 3800\mm^3 (4000–10 000), hemoglobin at 9 mg\dl (12–13), erythrocyte sedimentation rate at90 mm\h^1 (0–20), direct combs test was positive, complement: c3 value was low at 50 (80–170), and c4 value was low at 8 (10–40). Anti-DS DNA titer was positive, at 25 ur (20–40). Urine analysis revealed the presence of proteinuria and cylinders. 24 h urine analysis showed a proteinuria at 2340 mg, and creatinine at 690 mg.

Chest radiography showed bilateral effusion (Fig. 1), and thoracentesis was consistent with lupus.

A kidney biopsy showed grade III lupus nephritis (Fig. 2).


GROSS DESCRIPTION:

Received are fragments of tan white tissue submitted in part for IF and the remaining for light microscopy and special stains.

MICROSCOPIC DESCRIPTION:

The biopsy material comprises fragments of renal cortex containing forty glomeruli and seven are hyalinized. Ten glomeruli show the presence of segmental proliferative lesions with fibrinoid necrosis. Two show cellular crescents and two show segmental scars. The remaining glomeruli and uninvolved tufts show focally thickened glomerular basement membranes. The mesangial areas are expanded with PAS positive mesangial matrix and moderate hypercellularity (up to 5 cells/mesangial areas). The interstitium shows scattered inflammatory cells. The trichrome stains shows interstitial fibrosis involving 30% of the renal cortex. The tubules show focal apute tubular injury with loss of brush borders and thinned epithelium an red blood cell casts. The blood vessels show moderate subintimal fibrosis (25-50% occlusion of the lumens) The congo red stain is negative for amyloid

IMMUNOFLUORESCENCE STUDY:

Six glomeruli present in the sample examined and they show predominantly glomerular and mesangial deposition of IgG, kappa, Lambda, C3 and C1q (2-3+)

DIAGNOSIS:

NEEDLE BIOPSY; KIDNEY:

FOCAL PROLIFERATIVE GLOMERULONEPHRITIS CONSISTENT WITH LUPUS NEPHRITIS (ISN/RPS CLASS III) SEE COMMENT

COMMENT:

This is an active lupus nephritis cases with high activity index highlighted by the presence of focal necrotizing lesions involving 10/40 glomeruli with two crescents. The chronicity index is mild with the presence of interstitial fibrosis and vascular scarring with 2/40 glomeruli showing segmental scars.

Figure 2. Shows a result of renal biopsy.

She was given pulse methylprednisolone 1 g/iv/day for 3 days. After discussion with the patient and due to her financial inability to buy mycophetyle mycophenolate, it was decided to put her on intravenous cyclophosphamide monthly for 6 months, explaining its side effects, especially infertility and on the fetus, and the urine pregnancy test was negative, the HCG was normal.

When the patient revisited our department to receive the sixth pulse of cyclophosphamide dose, we noticed that she had a large abdomen, and she admitted that she had not told us that she had gotten pregnant in her third month.

The ultrasound of the fetus was normal. The gynecology consultation indicated abortion, but the patient refused, despite explaining to her the great risk of having malformations.

Cyclophosphamide was stopped and replaced by azathioprine with close monitoring of her and routine tests during pregnancy were performed such as CBC, ALT, AST, UR, CRP, erythrocyte sedimentation rate, CRP, and urinalysis tests for proteinuria, hematuria, and cylinders and they were normal. At close monitoring of the fetus every 35 weeks of gestation, she gave birth, and a healthy-looking boy was born, without any obvious congenital malformations, and by following up the child is alive and does not complain of any deformities or secondary neoplasms such as lymphoma, leukemia, and myeloproliferative disorders (Fig. 3).

We have performed electrocardiography and echocardiography and there were normal limits.

Our study is compatible with the surgical case report (SCARE) guideline checklist[13].

This case is submitted on the research registry dashboard at http://www.researchregistery.com.

Discussion

SLE affects females of reproductive age, who have normal fertility[2]. Our patient is 32 years old, with a diagnosis of SLE, 3 years ago.

Treatment of lupus during pregnancy can be a great challenge to the clinician: balancing the risk of harm to the fetus with the mother's health. However, the compatible medications available for the treatment of severe lupus during pregnancy are corticosteroids and azathioprine[14].

The first drug of choice for diffuse proliferative lupus nephritis remained cyclophosphamide, as it is reported its benefits in reducing both morbidity and mortality in SLE[5]. Although recent studies have shown similar outcomes with the treatment of lupus nephritis with mycophenolate mofetil (MMF), it is still in practice preferred Cyc, due to the inability to tolerate MMF[15].

In this case, we described a normal pregnancy in a woman exposed to Cyc during the first trimester of pregnancy, a crucial time in morphogenesis with a greater tendency toward malformations[16].

Lannes G *et al.*[17] a cohort study, showed that pregnancy is possible after Cyc therapy with a good outcome in two-thirds of cases. Whereas, Sen *et al.*[5] in their retrospective study showed that the risk of ovarian failure is impacted by the age of the patient at the time of exposure to the medication and dose of cyclophosphamide.

Cyc is known to be a teratogenic drug in animals[18]. In humans, the drug is detected in the amniotic fluid and classified as a pregnancy risk factor D drug, with evident risks to the fetus[19].

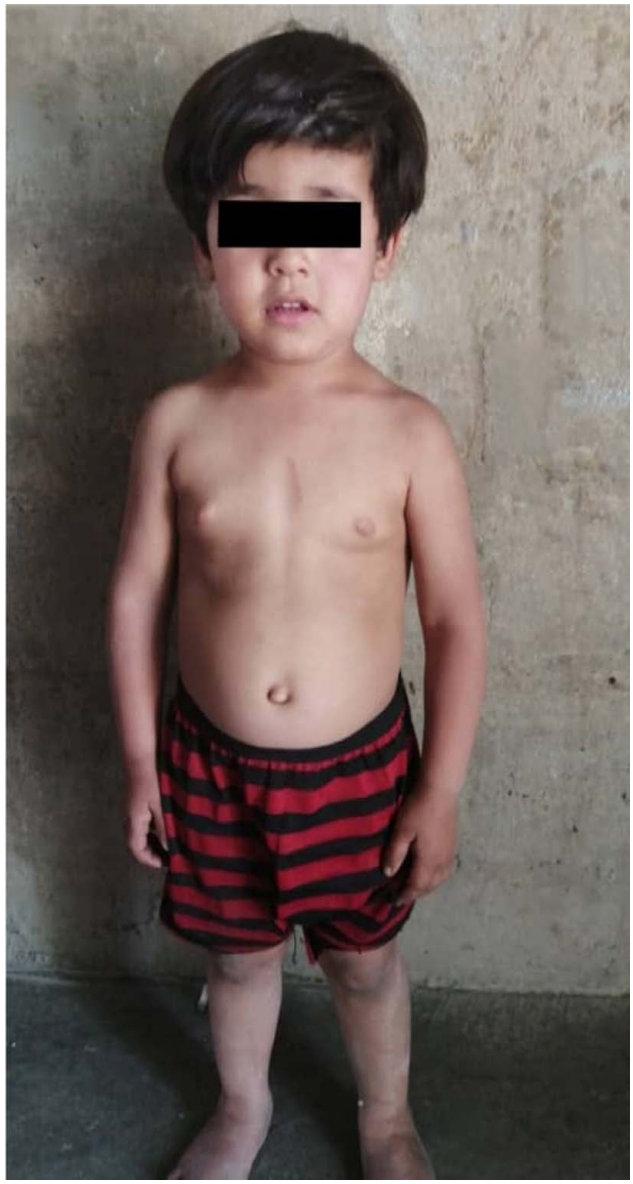


Figure 3. Show the child.

Cases of malformation have been described in newborns of mothers who received cyclophosphamide in the first months of pregnancy, as in our case. Nonetheless, its repercussion on fetal survival remains poorly comprehended[6].

Developmental delay, cleft palate, ear defects, microcephaly, absence of digits, and hypoplastic limbs were described as teratogenic effects of cyclophosphamide exposure, especially during the first trimester[20]. Our newborn boy had none of these malformations. However, late pregnancy exposure in the second and third trimesters appears to be less toxic to the developing fetus[6].

Actuality, there are few reports of healthy children born after their mothers have been exposed to Cyc during the first trimester of pregnancy, as in our case.

Another point that should be mentioned is the need to follow-up with the child in the future since cyclophosphamide has been reported to cause secondary neoplasms later in life following

exposure in utero[21]. In our case report, the child has not yet presented any complications, despite that the 17-month follow-up period may be considered insufficient for a definitive conclusion. Actuality, there are few reports of healthy children born after their mothers have been exposed to Cyc during the first trimester of pregnancy, as in our case.

Conclusion

Despite the possibility of successful pregnancies following Cyc exposure, this drug has been classified as teratogenic. Caution should be held in the decision of treatment with cycle patients at childbirth age.

Protection of human and animal subjects

No experiments were performed.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.
Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Ethical approval

This case report was approved by the ethical approval was given by the Ethical Committee of the Faculty of Medicine, Damascus University (N: KD 1994,2023).

Informed consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

Author contribution

T.D.: literature review, manuscript writing and editing, final manuscript review and approval, and clinical follow-up; M.I.A., R.T., G.H., and M.K.: obtaining informed written consent, clinical follow-up, manuscript writing, and approval of the final manuscript.

Conflicts of interest disclosure

All authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Tasneem Drie.
2. Unique identifying number or registration ID: research registry 8919.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com /browse-theregistry#home/.

Guarantor

Tasneem Drie. E-mail: samsomadrei@gmail.com.

Data availability statement

Datasets generated during and/or analyzed during the current study are publicly available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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