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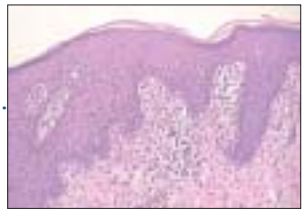

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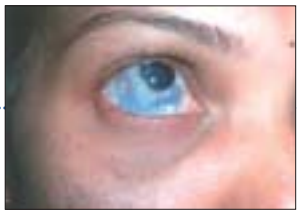

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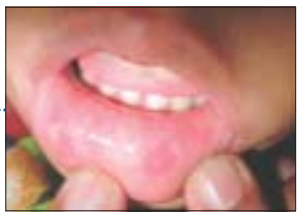

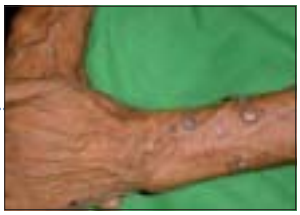

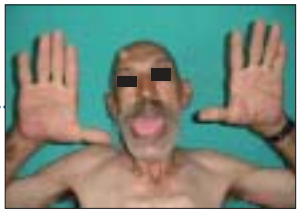

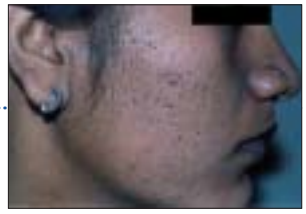

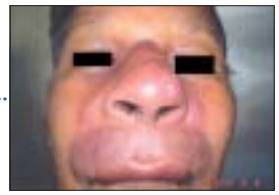

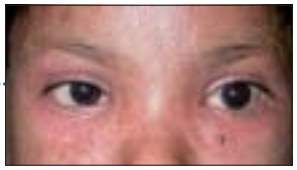

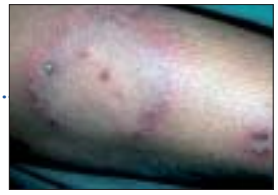

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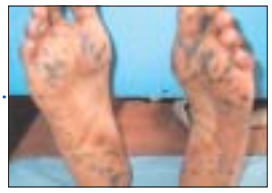

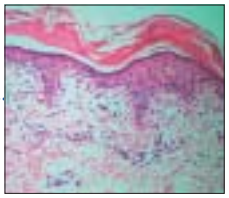

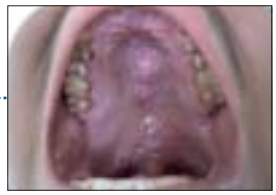

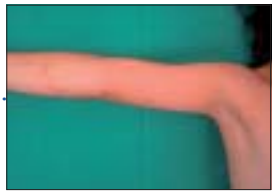

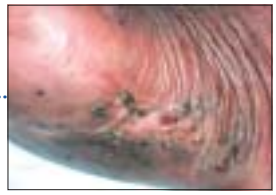

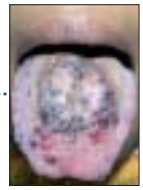

Premature ovarian failure due to cyclophosphamide: A report of four cases in dermatology practice

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ABSTRACT

Immunosuppressant drugs like cyclophosphamide are used in the treatment of a variety of skin disorders. Though it is a very useful drug, it has some serious side-effects. Prolonged amenorrhea due to premature ovarian failure leading to infertility is one of the serious side-effects of cyclophosphamide. Four cases of cyclophosphamide-induced premature ovarian failure are presented. Two patients of scleroderma, one patient of pemphigus and one patient of hypersensitivity vasculitis developed amenorrhea due to premature ovarian failure leading to infertility after receiving cyclophosphamide 50 mg OD for eight months to one year. The ages of these patients ranged from 28-38 years. All these patients had good improvement of their disease with cyclophosphamide. These patients did not experience any other side-effects and their routine blood and urine tests were normal. There were no spontaneous menses during the follow-up period of one to two years. Because of the serious risk of developing premature ovarian failure, cyclophosphamide should be avoided in those patients where the family is not complete.

Key Words: Cyclophosphamide, Dermatology, Premature ovarian failure

INTRODUCTION

Immunological mechanisms are involved in the pathogenesis of many skin diseases. In the absence of any identifiable cause, suppressing the clinical manifestations by using immunosuppressants remains the only treatment option. A variety of immunosuppressants are used in dermatology. Cyclophosphamide is used as an immunosuppressant in the management of pemphigus vulgaris, bullous pemphigoid, connective tissue disorders like systemic lupus erythematous (SLE), scleroderma, dermatomyositis, neutrophilic dermatoses like pyoderma gangrenosum, Behçet's disease, various types of vasculitis like Wegner's granulomatosis, polyarteritis nodosa, leukocytoclastic vasculitis, cryoglobulinemia and many other disorders. [1]

In many of these disorders, steroids are used for long term. To minimize the side-effects of long-term steroids, drugs like cyclophosphamide and azathioprine are used as steroid sparing agents. Cyclophosphamide though a very useful drug, has serious side-effects. Infertility caused by cyclophosphamide has not been adequately discussed in most of the textbooks. Four cases of premature ovarian failure induced by cyclophosphamide are presented.

CASE REPORTS

Case 1

A 28-year-old unmarried female was referred by a physician for scleroderma in June 2003. She had received intermittent steroids, antioxidants, nifedipine and aspirin without much relief. On presentation, she had severe acrosclerosis, Raynaud's phenomenon, shortening of fingers due to old gangrene and difficulty in swallowing solid food.

Diagnosis of scleroderma-CREST syndrome was made. Because of poor response to earlier treatment, cyclophosphamide 50 mg OD was started, along with one

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month course of steroids. By four months, the patient showed good improvement. There was no progression of the disease, even the sclerosis started improving. Cyclophosphamide was continued for one year without any side-effects. The disease showed steady improvement. After receiving cyclophosphamide for one year, she developed amenorrhea. After endocrinal evaluation she was diagnosed as having premature ovarian failure. Cyclophosphamide was discontinued in June 2004. The patient was stable without much problem for one and a half years. In February 2006 she presented with worsening of the disease. Steroid was started along with nifedipine and pentoxyphylline, without much improvement. In March 2006, seeing minimal response to treatment, she herself suggested starting cyclophosphamide again. Since premature ovarian failure had already occurred and there were no spontaneous menses even one and a half years after stopping cyclophosphamide and the disease was progressive, the patient was restarted on cyclophosphamide, nifedipine and aspirin in March 2006. By May 2006, there was significant improvement with no pain, no gangrene. Cyclophosphamide was continued for three months and discontinued in July 2006.

Case 2

A 29-year-old female patient presented in July 2003. She was diagnosed as scleroderma by a dermatologist in 2001 and was treated with topical steroid, antioxidants, and nifedipine for two years with minimal improvement. On examination, she had severe acrosclerosis, Raynaud's phenomenon with narrowing of fingers, shortening of multiple digits due to gangrene and difficulty in swallowing solid food. She was married four years back with three abortions in the last three years. Because of the severe and progressive nature of the disease, cyclophosphamide 50 mg OD along with one month course of steroid was started. Cyclophosphamide was continued. With treatment, the disease progression was arrested and by the third month the patient noticed improvement in acrosclerosis. In May 2004, after 10 months of cyclophosphamide therapy, the patient developed amenorrhea. Hence, cyclophosphamide was discontinued. After endocrinological work-up, she was found to have developed ovarian failure. She was symptomatically stable for one year. She never had spontaneous menses even two years after stopping cyclophosphamide. She was not willing to continue cyclophosphamide therapy in spite of her disease being gradually progressive.

Case 3

A 30-year-old married female presented in October 2002 with multiple blisters all over the body and oral ulcers of four months duration. On clinical and biopsy findings, diagnosis of pemphigus vulgaris was made. She was started on steroid and cyclophosphamide. Steroid was discontinued after six weeks and cyclophosphamide 50 mg OD was continued. In April 2004, as the disease was apparently under control, she discontinued cyclophosphamide on her own after completion of one and a half years of treatment. She noticed amenorrhea seven to eight months after starting cyclophosphamide treatment and had no spontaneous menses till last follow-up in July 2006 i.e. two years after stopping cyclophosphamide. In July 2006 she came back with relapse of pemphigus. She has a male child of seven years and wanted to restart cyclophosphamide to control the pemphigus.

Case 4

A 38-year-old female presented in November 2004 with recurrent palpable purpuric spots on extremities for eight to ten years. There was history of occasional abdominal pain but no joint pain. Skin biopsy showed vasculitis, blood count was normal, stool showed 3-4 RBCs /hpf. Urine examination showed albumin 1+ and 9-10 RBCs /high power field. A diagnosis of hypersensitivity vasculitis was made. Lesions improved with 20 days course of steroid but recurred after stopping steroid. She had received steroids in the past also with temporary improvement. Because of the effect of cyclophosphamide in other vasculitis, it was decided to start cyclophosphamide in December 2004. Lesions cleared with cyclophosphamide 50 mg OD, so it was continued. After eight months, in July 2005, cyclophosphamide was discontinued as the patient developed amenorrhea. Endocrinological workup revealed ovarian failure. Till the last follow-up in July 2006 i.e. one year after stopping cyclophosphamide, there were no spontaneous menses. She was married since 15 years without any issue. She had taken treatment for primary infertility seven years back. She had regular menses with normal hormone profile before starting cyclophosphamide. Ovarian failure developed in this patient after eight months of cyclophosphamide therapy.

DISCUSSION

Immunosuppressant drugs are used in many serious and chronic diseases in Medicine and Dermatology practice. Cyclophosphamide, azathioprine, and methotrexate are some of the drugs used commonly for immunosuppression. Cyclophosphamide is an alkylating agent that damages the DNA molecule which leads to either cell death or may cause mutagenesis and carcinogenesis.[1] Rapidly dividing cells like lymphocytes, other bone marrow derived cells, gonadal cells which replicate their DNA rapidly are maximally affected. Cyclophosphamide has more pronounced action

on B lymphocytes than T lymphocytes,[1] thereby making it more effective in controlling antibody-mediated diseases. Dexamethasone-cyclophosphamide therapy (DCP) is very popular in India and has been used in the management of a variety of diseases.

Amenorrhea lasting for more than 12 months after discontinuation of cyclophosphamide before the age of 45 years is considered as premature ovarian failure.[2] The effect of cyclophosphamide on fertility is not adequately discussed in most of the textbooks. Infertility due to ovarian failure is probably the most common and serious side-effect of cyclophosphamide occurring in 30-70% of women treated with cyclophosphamide[3] whereas other side-effects are uncommon in dermatology practice.

The Website of Johns Hopkins University on vasculitis indicates that the risk of infertility due to cyclophosphamide among women of childbearing age is 57%. In a study by Boumpas *et al.* sustained amenorrhea was seen in up to 39% of patients of lupus erythematosus receiving monthly high-dose intravenous pulse cyclophosphamide with a total of 12 or more pulses and the risk of amenorrhea increased with the age. Risk of developing sustained amenorrhea in patients younger than 25 years was 12%, between 26-30 years 27% and over 31 years 62%.[4] In the same study three patients with lesser number of pulses (seven pulses) had reversal of amenorrhea fewer than 12 months after cessation of therapy. In another study of 71 women of SLE aged 17-45 years, ovarian failure occurred in 11 (15%) patients. In patients who developed ovarian failure, the cumulative dose of cyclophosphamide was significantly higher (18.9g versus 9.1g).[5] In 84 women, 56 with SLE and 28 with other diseases like Wegener's granulomatosis and systemic vasculitis who received intravenous pulse cyclophosphamide, 23 women developed amenorrhea which was permanent in 19 women (13 with SLE and six with other disease) and the risk of ovarian failure correlated with the age of the patient and was independent of underlying inflammatory pathology.[6] Of 92 women with SLE treated with oral cyclophosphamide menstrual disturbances occurred in 55% of patients, 19% had oligomenorrhea and 36% patients developed amenorrhea which was permanent in 27% of patients and the frequency of amenorrhea were directly related with the age of the patients at the initiation of cyclophosphamide.[7] In one study from China, out of 138 females with SLE treated with cyclophosphamide, 46 developed ovarian failure.[8] Pasricha reported amenorrhea in about 50% of the female patients who received DCP for pemphigus.[9]

Out of 18 women who received cyclophosphamide for breast cancer, 15 developed permanent amenorrhea and women over 40 years developed amenorrhea after receiving cumulative dose of 5.2 g of cyclophosphamide whereas dose required to cause amenorrhea in young women was 9.5 g.[10] In three of these women who underwent therapeutic oophorectomy, on biopsy no ovarian follicle was seen indicating severe damage to gonadal cells. Cyclophosphamide is the most commonly implicated drug causing damage to oocytes and granulosa cells in a dose-dependent manner. Ultrastructurally it is associated with marked follicular loss. Oocytes are produced in ovaries at the time of fetal development. After birth, no new oocytes are produced. Hence the number of oocytes in adult female ovaries is limited and their loss is irrecoverable.[11] With age, there is progressive reduction in number of oocytes. Menopause results when the oocyte reserve of ovaries is exhausted.

Cyclophosphamide causes progressive and irreversible damage to oocytes in a dose-dependent manner,[12] thereby reducing the number of oocytes in ovaries. With high dose and longer duration, oocyte number is reduced drastically resulting in premature ovarian failure and those who do not develop premature ovarian failure are at risk of developing premature menopause in future due to reduced oocyte reserve.[12] Older women with low primordial follicle pool have higher risk of developing complete ovarian failure compared with young women with high primordial follicle number.[13] The age at the initiation of therapy and the cumulative dose are strong predictors of premature ovarian failure. Ovarian damage often manifests with amenorrhea, low estrogen level and increased FSH and LH, which resemble the hormonal changes seen at menopause.

Gonadal damage can be caused by cyclophosphamide, chlorambucil and busulfan.[13] Alkylating drugs are highly toxic even to male gonads. With cyclophosphamide therapy, there is progressive decline in sperm count leading to azoospermia within several months which may be irreversible. Azoospermia or severe oligospermia developed in 13 of 17 patients of Behçet's disease who received cyclophosphamide.[14] Because of serious risk of infertility, whenever possible, cyclophosphamide should be avoided in both males and females where the family is not yet complete. Most of the times cyclophosphamide is used in the treatment of serious diseases like connective tissue disorders and other autoimmune disorders which are associated with high morbidity and mortality and which mostly affect young females. Other immunosuppressants like azathioprine and methotrexate may be used in this situation; however, these drugs also cause serious side-effects.

Methotrexate and azathioprine, affect fertility temporarily. Ovarian failure causing infertility is not reported with both these drugs. Antimetabolites like methotrexate act by inhibiting DNA synthesis. It can affect only the dividing cells because only dividing cells replicate their DNA. Methotrexate acts only on the growing ovarian follicles. Methotrexate does not affect the dormant follicles.[15] Hence fertility is affected only as long as the patient is taking methotrexate. Once methotrexate is discontinued the dormant follicles can grow normally restoring the fertility. Alkylating agents like cyclophosphamide damage the DNA which results in cell death. Cyclophosphamide damages the DNA of dividing as well as of non diving cells. Cyclophosphamide destroys not only the growing ovarian follicles but also the dormant follicles in a dose-dependent manner,[15] resulting in a decrease of the ovarian reserve of oocytes/ovarian follicles. However, those ovarian follicles which escape the toxic effect of cyclophosphamide can lead to normal pregnancy after discontinuation of therapy, the risk of congenital malformation is not increased.[12]

The immunosuppressant action of cyclophosphamide may be more powerful than other drugs. Due to the serious nature of the disease if it is decided to start cyclophosphamide in young females whose family is not complete, patient should be counseled and the risk of infertility should be discussed with the patient. Amenorrhea may be reversible in early stages[4] hence the menstrual history should be regularly taken during follow-up visits and cyclophosphamide should be discontinued if patient develops amenorrhea. The only option for a patient who developed ovarian failure and desires a child is Assisted Reproductive Technique like oocyte/embryo donation.

Depot leuprolide acetate, a synthetic gonadotropin releasing hormone (GnRH) analog was found to be effective in protection against premature ovarian failure during cyclophosphamide therapy. Premature ovarian failure developed in one of 20 (5%) women treated with GnRH analog along with cyclophosphamide compared with six of 20 (30%) without GnRH in an age and dose-matched study.[16] Administration of contraceptive drugs during cyclophosphamide therapy also enhances survival of greater number of ovarian follicles though total ovarian protection is not assured.[13,17] Cyclophosphamide is more toxic to the rapidly dividing cells like gonadal cells. Proliferation of the gonadal cell is dependent on the Follicle Stimulating Hormone (FSH) secreted by the pituitary gland. When the proliferation of the gonadal cell is reduced by decreasing the amount of FSH by using either contraceptive drugs or GnRH, the effect of cyclophosphamide can be minimized thereby offering protection from ovarian failure. However, Whitehead *et al.* found no protective effect from combined oral contraceptive pills against cyclophosphamide-induced ovarian failure.[18]

Similarly, testosterone was also found to offer protection against azoospermia caused by cyclophosphamide in males. In 15 nephrotic syndrome male patients who were treated with cyclophosphamide for six to eight months azoospermia developed in all the patients but in five of these patients who also received testosterone along with cyclophosphamide sperm count returned to normal after six months.[19] Externally given testosterone suppresses FSH which reduces the spermatogenesis making it less susceptible for cyclophosphamide toxicity.

The dose of cyclophosphamide in all our patients was 50 mg OD and ovarian failure developed in these patients after eight to 12 months of therapy. Infertility is a very disastrous side-effect in young females, especially in traditional male-dominated societies. In all our patients, regular blood and urine examinations were within normal limits. During cyclophosphamide therapy regular blood counts are routinely done which can indicate early marrow suppression. In the author's experience it is not a very common side-effect with the dose of 50 mg OD. Bladder side-effects can be managed by sufficient oral intake and frequent voiding. For risk of developing cancers, patient can be regularly examined and kept under follow-up. Contraceptive pills may be added to minimize the risk of ovarian failure. Every drug will have side-effects but some side-effects can be disastrous for the patient. On the other hand, denying an effective drug in a life-threatening disease may also have disastrous consequences. Hence before starting a toxic drug like cyclophosphamide the risk benefit ratio should be considered and it should be used only if other less toxic therapies have failed.

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