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A RARE CYCLOPHOSPHAMIDE -ASSOCIATED LIVER TOXICITY IN A PATIENT WITH PAN-LIKE VASCULITIS: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Cyclophosphamide is an alkylating agent belongs to oxazaphosphorines. It can be prescribed both oral and intravenous and also in a wide ranges of dosage. However various reported side effects of the drug are the main reason to restrict the uses. Cyclophosphamide can be metabolized in the liver mostly by cytochrome p450 enzymes into to form 4-hydroxycyclophosphamide that has the chemotherapeutic characteristic. By metabolizing the parent molecule cytotoxic molecules can be derived such as acrolein which is well known to cause hepatotoxicity.

We report a 36 years old woman suffering from PAN-like vasculitis. Before the treatment she had normal liver function tests. The patient has been underwent the treatment by pulse methylprednisolone and pulse cyclophosphamide(500mg/m2). In the first two weeks of the therapy leucopenia and creatinine increscent occurred and in the third week of therapy she developed rise in liver enzymes. Hepatotoxicity was revealed by liver biopsy so cyclophosphamide was prescribed in the half of the previous dose but after

three weeks liver enzymes elevated again. Thus cyclophosphamide therapy was replaced with sodium rituximab administration.

Early recognition of liver toxicity and early drug withdrawal are the most important applications to choose the best strategy in order to diminish drug induced hepatotoxicity. Therefore accurate patients' medical profile must be provided carefully. In order to diagnose hepatoxicity, evaluating the liver enzymes accompanied by liver biopsy is strongly suggested. However new medications such as rituximab administration seems to be an effective method to prevent hepatotoxicity complications.

Keywords: Cyclophosphamide, Liver Toxicity, PAN-like Vasculitis

INTRODUCTION

Systemic vasculitides including polyarteritis nodosa, Churg Strauss syndrome, microscopic polyangiitis and Wegener's granulomatosis is characterized as inflammation and necrosis of blood-vessel walls that can affect all sizes of blood vessels from the aorta to capillaries. It has been revealed that steroids and immune suppressants can treat systemic vasculitides effectively. However, the therapeutic strategy differs from one disease to the other which should be adjusted due to the predictable outcome, severity, pathogenic mechanisms and patient's general condition (1).

Cyclophosphamide is an oxazaphosphorine-substituted nitrogen mustard (alkylating agent). Due to capability of the use in both conventional and high-dose regimens as well as oral and intravenous injections and also interfere with DNA replication, it is broadly used in chemotherapy to treat cancers, autoimmune disorders, and AL amyloidosis. Approximately 70–80% of the administered drug is converted primarily in the liver by cytochrome p450 enzymes into to form 4-hydroxycyclophosphamide (chemotherapeutic metabolite). Despite of effective influence it should be prescribed carefully based on patients' medical characteristics such as age, sex and determined needed dosage. If not lethal adverse consequences such as acute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and permanent infertility would have the chance to indicate (2-4).

Cyclophosphamide main effect of is due phosphoramide mustard by alkylating

DNA. These positively charged, reactive intermediates alkylate nucleophilic bases, resulting in the cross-linking of DNA and of DNA proteins, breaks in DNA, and consequently decreased DNA synthesis and apoptosis. One of the most important factors to let the metabolite to form is low levels of Aldehyde dehydrogenases (ALDH) in cells. The irreversible crosslinks formed by phosphoramide both between and within DNA strands at guanine N-7 positions leads to cell apoptosis (5, 6).

Despite the vast range of uses clinical application of cyclophosphamide is often restricted due to its serious adverse events as in following is mentioned: Hematologic, Including reversible leukopenia and neutropenia is common and dose dependent. Infection, it is frequent that a range of common and opportunistic pathogens cause infection. Urologic, the bladder toxicities, hemorrhagic cystitis, and bladder cancer have been reported referred to duration of therapy, and cumulative cyclophosphamide dose. Nonglomerular hematuria, from minor, microscopic blood loss to severe incidence and macroscopic bleeding, is the most common manifestation of cyclophosphamide induced cystitis. Malignancy, taking Cyclophosphamide increases the risk of malignancies. Reproductive, its use may results in significant gonadal toxicity. Pulmonary, pulmonary toxicity occurs in less than 1% of patients. Miscellaneous, a varying degree of reversible alopecia can occur with daily oral and monthly pulse cyclophosphamide (6).

The parent molecule is not cytotoxic itself but when it is metabolized in the liver, it converts to active and inactive cytotoxic metabolites (acrolein for instance) leading to hepatotoxicity. Acrolein may cause liver dysfunction by binding to cytochrome enzymes, hepatic macromolecules and nucleic acids (7).

Because of a unique metabolism in hepatotoxicity and relationship to the gastrointestinal tract, the liver is an important target of the toxicity of drugs, xenobiotics, and oxidative stress.

Drugs and xenobiotics are commonly lipophilyc and capable to cross from gastrointestinal cell membrane. They are absorbed by the abdomen and carried by the portal vein which comes directly from the gastrointestinal viscera and spleen and the liver is their direct target in concentrated form. These toxicities are

likely the cause of the unique vascular, secretory, synthetic, and metabolic features of the liver that could be detoxify by drug-metabolizing enzymes (8).

Drug-induced hepatotoxicity that could lead to injury and liver failure may result in liver transplantation or death.

In addition to received dose, age, sex and body mass index are the most important factors that can affect liver metabolism (9).

Drug-related hepatotoxicity occurs rarely for many drugs which incidences between 1 in 10000 and 1 in 100000 patients. Hepatotoxicity on the other hand can commonly lead to removing of these therapeutic drugs from the commercial market and it represents the most important cause of the non-approval and withdrawal of drugs by the food and drug administration (10).

For most cases the best alternative is to stop the treatment and only confine on the general medical cares because continuing the treatment develops the risk of liver failure effectively which is the leading cause of acute liver failure among patients referred for liver transplantation that surprisingly most of whom had no prior background of hepatic disease (11).

Etiology of drug-induced hepatotoxicity are mostly referred to metabolic, genetics and immunological characteristics of the patients separately or/and in concert. Some investigators have divided those generally into two broad categories. The first consisted of toxicity as a consequence of the drug itself or by one of its metabolites. The second mostly described as idiosyncratic in recent years, has been categorized into host-dependent and host-independent divisions. Genetic and metabolic causes are categorized in the host-dependent division however metabolic causes could be described either independently or in association with a genetic capacity. The host-independent division consisted of immunologic causes (12).

Alternative diagnoses such as hepatitis B, C, and E, CMV, EBV are more likely to happen prior to the drug-induced hepatotoxicity suspicion (13).

Case presentation

We reported a 36 years old woman who suffered from vasculitis in mesenteric vessels (PAN-like vasculitis) which was indicated by Ilium biopsy result. She had normal liver function tests (LFT) before the treatment was begun. As of vasulitis diagnosis she has been underwent the

treatment by pulse methylprednisolone (1 g/day for 3 days) and pulse cyclophosphamide (500 mg/m^2). After 2 weeks of cyclophosphamide therapy leucopenia (WBC= 1500) and creatinine increscent (3.6 mg/dL) occurred which by taking granulocyte-colony stimulating factor (G-CSF) and adequate hydration WBC and Cr level were adjusted to normal range. But in the third week of therapy she developed rise in liver enzymes as follow: AST= 650, ALT= 239 and AP= 1056. Considering hepatotoxicity as one of seldom adverse reactions of cyclophosphamide therapy, examinations were approached to evaluate viral infections and autoimmune hepatitis and also liver ultrasonography and Medicare remit easy print (MREP) were applied which they revealed of nothing unmoral and the results seemed to be OK. Liver enzymes level remained high for 6 weeks after interruption of cyclophosphamide treatment and there was no reasonable justification for that so liver biopsy was applied.liver sonography,MRCP,AntiLKM1,ANA,ASMA,Viral markers were normal. By a liver needle biopsy it was revealed that liver specimen consisted of 3 cores of gray- cream soft tissue measuring 1.8cm in total length and 0.1cm in maximum diameter. Then via staining the sections by HE, Trichrome, PAS and reticulin methods, preserved lobular architecture and the following histological changes were indicated: the available portal spaces were normal looking with respect to the connective tissue stroma, bile ducts and vascular channels. No inflammation or interface damage was observed as well as for fibrosis. The lobular architecture of liver samples was preserved. Central veins and hepatic sinusoids as well as the hepatic cord and reticulin framework were within normal limits. No lobular inflammation was seen. Mild swelling of parenchymal hepatocytes was observed throughout the biopsy sample. No steatosis or bilirubinostasis were seen. The glycogen seemed to be moderately decreased. Due to the results drug toxicity was proposed. From 8^{th} week liver enzymes commenced to be decreased (AST= 70 and ALT= 130). However according to the disease essence we had to follow cyclophosphamide treatment. This time cyclophosphamide was prescribed in half of previous dose. After one week of prescription liver enzymes were increased more than three times again. According to this

circumstance we were obligated to change the therapy and sodium rituximab was prescribed instead.

DISCUSSION

We report a case of hepatotoxicity 3 weeks after pulse cyclophosphamide. Due to our patient's medical background cyclophosphamide is the most recommended cause of the hepatotoxicity. In general hepatotoxicity by cyclophosphamide administration occurs rarely and it is not well described. Honjo et al. reported a transient elevation of aminotransferase serum levels in 43% of the patients treated with cyclophosphamide. However in the mentioned study the transient elevation of transaminases was not proved to be the main and only cause of the administration of cyclophosphamide. As all the patients received a combination of antineoplastic agents, several of which are known to be hepatotoxic and at the time of the study screening for hepatitis C was not possible. Concomitant use of other drugs was not mentioned as well and the possible confounding factor of alcohol intake was not evaluated too (14).

Based on literature oral cyclophosphamide has been successfully introduced to control disease. Optimum treatment duration with cyclophosphamide is less than 1 year. It should be mentioned that shorter therapeutic protocols were evaluated to reduce toxicity resulting from prolonged cyclophosphamide therapy, and for severe PAN, a prescription of 12 pulses of cyclophosphamide provided better control; and fewer relapses and deaths occurred. The cyclophosphamide pulse dose was recommended previously 0.6 g/m^2 delivered monthly for maximum 1 year and the content of each pulse, as well as the total number and frequency of the pulses, should be adjusted according to following factors: the patient's condition, renal function, hematological data and the disease's response to prior therapies, including previous cyclophosphamide pulses (1). According to this our patient's circumstance was so unique that in very low-dose hepatotoxicity was proved.

White blood cells have been reported to be decreased by cyclophosphamide therapy. Among them lymphocytes are affected mostly and Lymphocytopaenia was evident within 24 h of a single dose and became more severe over 1 week. Granulocytopaenia becomes apparent within 10 to 21 days and finally

Haematological recovery is achieved in 4 to 6 weeks (15). Our study complied this as well however WBC decrement occurred after two weeks.

Duh et al reported that drug induced liver injury was the most common cause of liver enzyme abnormalities (40.6 cases per 100,000 persons per year) (16) so biochemical tests of liver function (AST, ALT, bilirubin, AP, prothrombin time or albumin) and histological findings (biopsy) are commonly reliable screening methods in order to diagnose hepatotoxicity. While some imaging techniques of the liver including radionuclide scan, ultrasound examination, computed tomography and magnetic resonance imaging cannot particularly predict early liver disease. Therefore, they just remain as complementary techniques to diagnose patients with elevated liver tests.

It has been indicated in addition to synthetic pharmaceuticals, herbal metabolites can cause hepatotoxicity as well. In a study on 16 patients suffering from herbal hepatotoxicity serum activities of ALT and AST were increased with an average of 1.435 U/L and 730 U/L in order. And also in 14 patients AP increased with average of 353 U/L. in these patients enzymes level normalization was not observed generally (17). Hepatotoxicity induced by cyclophosphamide has been reported previously as follows: in a report of one patient with two episodes of hepatic dysfunction associated with oral cyclophosphamide administration with systemic rheumatic diseases by Goldberg and Lidsky (18), a study by Mok and et al investigated continuous low- dose cyclophosphamide therapy (19), cyclophosphamide - induced hepatotoxicity in a patient with Wegener's granulomatosis by Snyder and et al (20) and also a study by Aakay and et al who reported a 40 years male patient under the treatment of oral cyclophosphamide (100 mg/d) for 45 days (21). Their findings revealed the therapy affected the serum characteristics as follows: an albumin of 3.3 mg/dL, globulin 2.9 mg/dL, alkaline phosphatase 206 U/L, aspartate aminotransferase 1806 U/L, alanine aminotransferase 2407 U/L. Even in a study by Subramaniam and et al it was indicated that after 24 hours of administration of low-dose intravenous cyclophosphamide (200 mg) hepatotoxicity may occur (22).

The active metabolites of cyclophosphamide lead to oxidative stress exhibited a catastrophic effect on hepatocellular membranes and destructive capability of target tissues. Subsequent damages to the tissues and inflammations result in liver enzyme elevation and can be assessed by biochemical tests as well as biopsies. Therefore using natural antioxidant compounds such as Ginseng (which is demonstrated that it alleviates cyclophosphamide -induced hepatotoxcity via two main pathways, GSH metabolism and primary bile acids synthesis (23)), and other hepatoprotective agent such as 18β-Glycyrrhetinic acid can be beneficial to reduce cyclophosphamide side effects (24).

As today vasculitis is known as a chronic disease, many investigations have been applied to improve treatment-related toxicity, reducing relapses and providing alternative treatments for refractory disease. During past decade cyclophosphamide and high-dose glucocorticoids are replaced by Rituximab, an anti-CD20 B cell-depleting therapy that offers a significant advance in the treatment of these diseases (25, 26).

CONCLUSION

Hepatotoxicity induced by medicines is generally a complicated circumstance that does not happen so often but when it does the drug is more likely to be removed from the markets. A complete resolution of symptoms can be achieved by early recognition of liver toxicity and early drug withdrawal. For this obtaining a detailed history about recent medication change through examinations and even questionnaires can be taken advantage. Better and more effective treatments are always incoming. However side effects of using present medications can be moderated by taking advantage of other compounds such as antioxidants. Meanwhile new therapies are more recommended.

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