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CASE STUDY

Chronic Myeloid Leukemia (CML), A Rare Adverse Effect of Cyclophosphamide

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ABSTRACT
Wegener's granulomatosis (WG) is a systemic disorder that involves both granulomatosis and polyangiitis with unknown risk factor. Cyclophosphamide and high dose corticosteroids are used for WG treatment as a standard strategy. Cyclophosphamide is mainly used in chemotherapy. This compound is one of the oxazaphosphorine group member and is an alkylating agent of the nitrogen mustard type. Like all other drugs, cyclophosphamide has unfavorable side effects such as acute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and permanent infertility. The aim of this case presentation is introducing a patient with WG whom suffer from chronic myeloid leukemia as cyclophosphamide therapy side effect. A 63 years old male patient with WG received cyclophosphamide (100 mg pill) and prednisolone for 2 years. After that, the continued treatment was conducted by mycophenolate mofetil and prednisolone. 3 years later the patient returned to the hospital with fever and myalgia. According to probable risk of mycophenolate mofetil this medical method was discontinued and alternative treatment approach by granulocyte-colony stimulating factor (GCSF) was began. The results of tests, include blood culture, urine culture, chest radiography, and ultrasonography of abdomen and pelvis were normal. The preformed flow-cytometry of bone marrow samples showed positive BCR/ABL which indicate CML in this patient. Besides the therapeutic effects, each drug has side effect as well. AML is one of the severe adverse effect of cyclophosphamide. However in this report, CML was introduced as a side effect of this medicine which is rare. The report shows that checking the rare complications such as CML would be helpful in therapeutic approach of these patients.

***Keywords**: Wegener's granulomatosis, Cyclophosphamide, Acute myeloid leukemia (AML), Chronic myeloid leukemia (CML)*

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) which was known as Wegener's granulomatosis (WG) formerly [1], is a systemic disorder that involves both granulomatosis and polyangiitis. This disorder is a type of vasculitis has effects on small- and medium-size vessels in various organs. GPA damage to the lungs and kidneys is so serious and can be fatal. It requires long-term immunosuppression [2]. The main causes of this disease are unknown, although bacteria and viruses, as well as genetics have been implicated in its pathogenesis [3, 4]. Cyclophosphamide and high dose corticosteroids are used for GPA treatment as a standard strategy. This combination is used to remission induction and less toxic immunosuppressants like azathioprine, leflunomide, methotrexate or mycophenolate mofetil. Trimethoprim/sulfamethoxazole also used due to its probable effect on relapse prevention [5]. Thanks corticosteroids and cyclophosphamide, 5-year survival is over 80% nowadays [3]. Long-term complications are common (86%), mainly chronic kidney failure, hearing loss and deafness [2].

As it mentioned before, prescribing cyclophosphamide is a standard therapeutic strategy for GPA patients. Cyclophosphamide is mainly used in chemotherapy. This compound is one of the

oxazaphosphorine group member [6] and is an alkylating agent of the nitrogen mustard type [7]. An alkylating agents add an alkyl group to N7 of guanine imidazole ring. Due to this alkylation intra-strand DNA crosslink would be formed which inhibit DNA replication [8]. Cyclophosphamide is effective drug to treat cancers, autoimmune disorders, and AL amyloidosis. To gain chemotherapeutic activity, cyclophosphamide as a prodrug will be converted to 4-hydroxy cyclophosphamide by liver cytochrome P450 (CYP) enzymes [9]. In addition to the favorable therapeutic effects, cyclophosphamide, like all other drugs, has side effects which are unfortunately severe and life-threatening adverse effects. These side effects include acute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and permanent infertility, especially at higher doses [10].

Leukemia is a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its acute and chronic forms. Additionally, the diseases are subdivided according to which kind of blood cell is affected. This divides leukemias into lymphoblastic or lymphocytic leukemias and myeloid leukemias. In acute myeloid leukemia (AML) which is one of the life-threatening adverse effects of cyclophosphamide treating, replacement of normal bone marrow with leukemic cells can be seen. This replacement causes a reduction in red blood cells, platelets, and normal white blood cells [11]. In addition, chronic myeloid leukemia (CML) is a cancer of the white blood cells. In this type of leukemia predominantly myeloid cells will be the increased and will have unregulated growth in the bone marrow and accumulated in the blood. CML is a clonal bone marrow stem cell disorder in which a proliferation of mature granulocytes and their precursors is found [12].

As it stated above, AML is one of the severe adverse effects of therapeutic approach by cyclophosphamide and there is a few reports to present CML as side effect of this treatment. According to this, it has been tried to introduce a patients with WG whom suffer from CML as cyclophosphamide therapy side effect.

CASE PRESENTATION

This case report introduce a 62 years old male patients suffered from WG with sinus, lungs, and kidney conflict from 2010. The kidney biopsy of this patient showed focal proliferative pauci-immune crescentic glomerulonephritis and cytoplasmic antineutrophil cytoplasmic antibodies (CANCA) 200 (10). The chosen therapeutic strategy for this patient was oral cyclophosphamide (100 mg pill) and prednisolone in the first 2 years. After that, the continued treatment was conducted by mycophenolate mofetil and prednisolone.

In April, 2015, the patient returned to the hospital with fever and myalgia. The only issue that observed in primary examination was pale conjunctiva. Further investigations showed pancytopenia in this patient. The primary possibility was pharmaceutical pancytopenia due to mycophenolate mofetil taking. According to probable risk of mycophenolate mofetil this medical method was discontinued and alternative treatment approach by granulocyte-colony stimulating factor (GCSF) was began. The results of this alternative therapeutic strategy did not show any improvement in pancytopenia. In the next step, the infection causes of pancytopenia was evaluated and the obtained results did not indicate the infection as a main cause of this disorder. The results of other tests, include blood culture, urine culture, chest radiography, and ultrasonography of abdomen and pelvis were normal as well. The peripheral blood film (PBF) showed content reduction in all three blood cell lines without any abnormal cells.

At final diagnostic step, needle aspiration biopsy and bone marrow biopsy were used. Aspiration did not show any significant result except reduction in cell lines content and bone marrow biopsy did not illustrate any important results as well. The preformed flow-cytometry of bone marrow samples showed positive BCR/ABL which indicate CML in this patient.

DISCUSSION

Along with desired effects of cyclophosphamide, this drug has adverse effects, like other drugs, as well. The adverse effect of this drug related to cumulative medication dose. Chemotherapy-induced nausea and vomiting, [13] bone marrow suppression, [14] stomach ache, hemorrhagic cystitis, diarrhea, darkening of the skin/nails, alopecia or thinning of hair, changes in color and texture of the hair, and lethargy are some of its side effects. Other side effects may include easy bruising/bleeding, joint pain, mouth sores, slow-healing existing wounds, unusual decrease in the amount of urine, or unusual tiredness or weakness [15].

Due to carcinogenic potential of cyclophosphamide the risk of some disorders such as developing lymphomas, leukemia, and skin cancer, transitional cell carcinoma of the bladder or other malignancies will be increased [16]. It was showed by Radis et al that 5 of 199 rheumatoid arthritis patients suffered from myeloproliferative neoplasms, including acute leukemia, non-Hodgkin lymphoma, and multiple myeloma within the first decade after receiving cyclophosphamide, however, they reported one case of

chronic lymphocytic leukemia in 119 rheumatoid arthritis patients without a history of cyclophosphamide use. [17] It has been believed that secondary acute myeloid leukemia will be occurred either by cyclophosphamide inducing mutations or selecting for a high-risk myeloid clone [18]. This risk may be dependent on dose, treatment modalities used (including radiotherapy), treatment intensity, and length of treatment. Cyclophosphamide-induced AML typically presents some years after treatment, with incidence peaking around 3–9 years. After nine years, the risk has fallen to the level of the regular population. When AML occurs, it is often preceded by a myelodysplastic syndrome phase, before developing into overt acute leukemia [19]. Cyclophosphamide-induced leukemia will often involve complex cytogenetics, which carries a worse prognosis than de novo AML [20].

In patients with hematuria and reduction of blood cells content after cyclophosphamide use history, the secondary malignancy related to this drug should be considered. Acute leukemia of myelogenous or lymphocytes are more prevalent following the use of cyclophosphamide [21]. But in this case report article chronic myeloid leukemia is introduced as a life-threatening adverse effect of using cyclophosphamide in WG patient which should be considered all the time.

Most of malignancies after taking cyclophosphamide are late complications and these side effects may even appear several years after discontinuing the drug. As it has been reported in this paper, CML, as an adverse effect of treatment with cyclophosphamide, reported 3 years after discontinuing the treatment by this drug. It should be considered that in case of any significant complications which are not associated with patients and disease activities, malignancies and infections should be examined.

CONCLUSION

Previously, AML was reported as one of the adverse effects of cyclophosphamide but in this case report we present a patient suffer from CML as a side effect of this medication which is rare case. According to this report, it should be noted checking the routine side effects of this medicine is not adequate and the risk of developing other rare complications, such as CML, should be considered in these patients as well.

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