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Case Report

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Reversible therapy-related dysplastic hematopoiesis following Beta Interferon Therapy in Multiple Sclerosis Patients: Report of 2 Cases

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Abstract

Background: Interferon beta-la and -1b have been increasingly used for the treatment of multiple sclerosis (MS). The most frequent systemic adverse effects are flu-like symptoms. Laboratory abnormalities include asymptomatic leukopenia and elevated hepatic transaminases. Myelodysplastic Syndrome (MDS) refers to a spectrum of hematological disorders which can occur in different situations. Several hematological abnormalities have been reported following interferon therapy.

Methods: We report two cases of secondary MDS after long term interferon therapy by using the laboratory data and bone marrow results.

Conclusion: Both of our cases were reversible; although treatment with IFNβ-1a and-1b is safe and well tolerated in the majority of population, we should be careful about this premalignant hematological disorder.

Introduction

Disease -modifying agents (DMAs), including interferon beta (IFNβ) and glatiramer acetate (GA), are amongst the mainstays of long-term treatments for multiple sclerosis (MS) [1]. Interferon beta-la and -1b reduce the frequency and severity of clinical exacerbations, and decrease both T2 weighted lesions and contrast-enhanced MRI activity in patients with MS [2]. Several biological activities of IFN-β have been highlighted, including its inhibitory effects on proliferation of leukocytes and antigen presentation [1,3]. Furthermore, IFN-β may modulate the profile of cytokine production towards anti-inflammatory phenotype both in the systemic circulation and within the CNS. Finally, IFN-β can reduce T-cell migration by inhibiting the activity of T-cell matrix metalloproteinases [3].

Therapy-related dysplastic hematopoiesis refers to a heterogeneous group of closely related clonal hematopoietic disorders that are characterized by hypercellular or hypocellular marrow with impaired morphology and maturation (dysmyelopoiesis) and peripheral blood cytopenias, resulting from ineffective blood cell production [4].

The diagnosis of therapy-related dysplastic hematopoiesis or MDS (acquired dysplastic changes) is made when the evaluation of the peripheral blood and bone marrow demonstrates morphologic, immunophenotypic, and cytogenetic changes.

MDS should be considered in any patient (more particularly, in the elderly patients) with unexplained cytopenia(s). Careful inspection of the peripheral blood smear and bone marrow aspirate is necessary to document

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the dysplastic cytological features identifiable in any or all of the hematopoietic lineages.

Potentially contributing conditions must be excluded. Various factors have been associated with acquired dysplastic changes; these include nutritional status, alcohol and drug use (medications such as valproic acid, mycophenolate mofetil, ganciclovir, alemtuzumab), occupational exposure to toxic chemicals prior to treatment with antineoplastic agents or radiotherapy, and risk factors for treatment of human immunodeficiency virus (HIV) infection [5].

Many patients with MDS, or acquired dysplastic changes, have macrocytic red cells, reduced reticulocyte percentage, and pancytopenia (anemia, leukopenia, and thrombocytopenia). These findings may also appear in the megaloblastic anemias. While granulocytes commonly display reduced segmentation, the so-called pseudo-Pelger-Huet abnormality, often accompanied by reduced or absent granulation is a characteristic of MDS [5].

Herein, we report two cases of relapsing MS that were treated with beta interferon, without any previous exposure to cytotoxic or chemotherapeutic agents or other predisposing conditions that developed a reversible type of dysplastic hematopoiesis years after initiation of beta interferon therapy.

Case Report

Case 1

A 39-year-old woman suffering from acute paresis of the right lower limb was referred to our clinic for evaluation. She had the symptoms for 8 years and the year before the evaluation, she had an episode of left optic neuritis which had been treated with high dose of steroids. She had recovered completely after 1 month. Neurological examinations revealed diplopia, limb ataxia, dysarthria and fairly clumsy tandem gait.

Given her history of two attacks, as well as MRI lesions matching the McDonald criteria for dissemination in space and time, other possibilities were ruled out and she was diagnosed as MS and accordingly, interferon β1b was started for the patient.

She had received interferon for 5 years without any significant side effects or unpredictable problems. During this period, she had 4 relapses for which she was treated with methyl prednisone pulse for each relapse. A few months prior to the time of this report, during routine evaluation of the patient, the lab data showed a reduction of WBC, Hb and platelets (WBC: $3000_{/dl}$, Hb: $9.8g_{/dl}$, PLT: $151/000_{dl}$- 2008/4). The interferon was stopped and hematology consultation was performed.

Bone marrow examinations showed dysplastic hematopoiesis, granulocytes displayed reduced segmentation (pseudo-Pelger-Huet abnormality) and reduced granulation.

The patient was treated with conservative therapy and gradually all hematologic measures returned to normal levels. The same beta interferon treatment was reintroduced. After more than 1 year of restarting the interferon treatment there were no abnormalities in the blood tests (WBC: 6900_{dl}, Hb: $10g_{/dl}$, PLT: 301.000_{dl}- 2010/10).

Case 2

A 35-year-old woman, with no significant previous illness, had a history of five-day diminished vision in the right eye followed by full recovery that had occurred seven years ago. Two years following the incident, she was apparently suffering from paresthesia and weakness in both lower limbs with left side predominance. Since MRI of the brain was compatible with MS, after ruling out other possibilities, she was diagnosed with a case of relapsing MS, for which she was treated with a course of intravenous methyl prednisolone over five days. Two years later, during laboratory follow up, the CBC showed a decrease in WBC and hemoglobulin levels (WBC: 2900_{dl}, Hb: $9/9_{g/dl}$, platelet: 168.000_{dl}). Interferon was stopped and hematology consultation was performed.

Bone marrow examinations confirmed dysplastic hematopoiesis; granulocytes displayed reduced segmentation (pseudo-Pelger-Huet abnormality) and reduced granulation.

After treatment with conservative therapy, gradually all hematologic measures returned to the normal levels (WBC: 4000_{dl}, Hb: $11.1g_{/dl}$, PLT: 193.000_{dl}- 2010/10). Beta interferon was restarted and after two years, no abnormalities have been observed in the blood tests.

Discussion

Beta Interferon is the first specific disease-modifying therapy approved in MS and also the most commonly prescribed agent worldwide. However, it has a modest effect in reducing relapse rates and MRI activity. Many patients are unable to tolerate it due to the associated side effects and/or mode of administration [6].

Thrombocytopenia, anemia, leucopenia, or an increase in liver enzymes may not infrequently develop at any time during therapy with these agents [7].

According to the published review articles, we did not find any reported case of dysplastic hematopoiesis following beta interferon therapy in MS until the preparation of this report. To date, only one case of secondary myelodysplastic syndrome (MDS) following long-term treatment with azathioprine in a patient with MS has been reported [10].

Dysplastic hematopoiesis (early & secondary MDS) is thought to arise from mutations in the multi-potent bone marrow stem cells, but the specific defects responsible for these diseases remain poorly understood [5].

Anemia dominates the early course. Most symptomatic patients complain about the gradual onset of fatigue and weakness, dyspnea, and pallor, but at least half the patients

are asymptomatic and their MDS is discovered only incidentally during routine blood counts [8].

These general symptoms are observed frequently in MS patients and we believe that the best way to verify dysplastic hematopoiesis is by laboratory-based bone marrow examinations.

The incidence is probably increasing as the age of the population increases. Therefore, it has been proposed that the incidence in patients over 70 years of age may be as high as 15 cases per 100,000 per year [9].

To the best of our knowledge, two cases of patients reported here are the first to have suffered from dysplastic hematopoiesis after beta interferon therapy. Dysplastic hematopoiesis in our patients may be primary; however, we should note that the age of initiation of primary MDS is somewhat higher our patients' age. The duration of interferon therapy may be important in inducing MDS. Both of our patients have been receiving interferon for more than 5 years. We are uncertain about the precise relationship between beta interferon therapy and MDS; however, we must be careful about the presence of such pre-malignant disease in any MS patient treated with beta interferon who has shown reduction in all hematologic elements in primary blood laboratory test.

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