Pancytopenia associated with clonazepam: a case report and a review of the literature

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Abstract

Background: Several psychotropic medications can mediate clinically significant hematologic dyscrasias, such as acquired aplastic anemia, severe neutropenia and thrombocytopenia. Agranulocytosis is a well-known adverse effect of clozapine, one of the atypical neuroleptic agents, with a cumulative incidence of 0.8%/year. Occurrences of benzodiazepine-induced thrombocytopenia, with detection of drug-dependent platelet antibodies, and thrombocytopenia secondary to clonazepam, a benzodiazepine derivative, have been documented in the literature. However, there are yet no reported cases of pancytopenia related to clonazepam.

Case presentation: We present a case of a 47-year-old Asian female with end stage renal disease and chronic anemia on hemodialysis. Clonazepam was prescribed for myoclonus disorder approximately two weeks prior to her hospitalization. Subsequently, she was hospitalized for neutropenic fever with thrombocytopenia and worsening anemia. Concurrent bone marrow examination demonstrated a markedly hypocellular marrow (10-20% total cellularity) for her age. Clonazepam was discontinued, with gradual improvement of thrombocytopenia and neutropenia in 1-2 weeks. To our knowledge, this is the first reported case of pancytopenia associated with clonazepam.

Conclusion: It is vital that clinicians conscientiously monitor patients when prescribing clonazepam. Thorough clinical evaluation and regular complete blood count analyses are imperative in preventing fatal hematologic adverse effects. Clonazepam must be included in the patient's drug allergy list once clinically significant clonazepam-associated pancytopenia is established.

Case presentation

A 48-year-old Asian female with end-stage renal disease on hemodialysis and chronic anemia presented with fever and chills and was subsequently found to have new-onset pancytopenia. Approximately two weeks prior to admission, she was started on clonazepam 0.25 mg twice a day for myoclonus. Her other medications included erythropoietin 2,000 U three times a week, felodipine 5 mg daily, aluminum hydroxide 500 mg three times a day, calcium carbonate 500 mg three times a day, labetalol 100 mg twice a day, folic acid 1 mg daily, and daily vitamin B complex. Blood culture was obtained which showed no growth of microorganisms after seven days of incubation. Analyses for human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) infections were negative. Antinuclear antibody (ANA) study was also non-reactive. The complete blood count (CBC) showed WBC of 386/μL (absolute neutrophil count of 49/μL), hemoglobin of 8.17 g/dL (MCV 91.2 fl), and platelet of 62,300/μL. Bone marrow biopsy and aspiration was performed to further evaluate the etiology of pancytopenia, which revealed a moderately hypocellular marrow with 10-20% total cellularity (Figs 1a and 1b). No aggregates of blasts or atypical cells were identified. A review of the patient's medications suggested that clonazepam, which was added to her regimen two weeks prior to admission, most likely precipitated the significant pancytopenia. Clonazepam was then discontinued, with gradual improvement of thrombocytopenia and neutropenia in 1-2 weeks. Afterwards, she has no recurrent pancytopenia.

Discussion

Although rare, blood dyscrasias, such as acquired aplastic anemia, leukopenia and/or thrombocytopenia have been established in some of the atypical or second generation antipsychotics, benzodiazepines, and other psychotropic agents [1]. For instance, agranulocytosis, with a 0.8%/year cumulative incidence and an estimated 1:10,000 death risk, is a well-recognized adverse effect of clozapine, one of the atypical neuroleptic agents [2]. Cases of thrombocytopenia from clonazepam, a benzodiazepine derivative, have also been described [3-5]. However, there are yet no reported occurrences of pancytopenia associated with clonazepam in the literature. Our patient, with end-stage renal failure, developed myoclonus while undergoing dialysis and was subsequently treated with clonazepam. She developed significant pancytopenia within two weeks of starting the medication. Probable viral infections, such as HBV, HCV, and HIV, underlying autoimmune disorders, paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome, and congenital marrow aplasia, were taken into consideration since these conditions may also promote pancytopenia or acquired aplastic anemia [6]. Discontinuation of clonazepam resulted in gradual rise of her WBC and platelet counts, which approached normal levels within one to two weeks. To the best of our knowledge, our case represents the first documented event of clinically significant clonazepam-associated pancytopenia.

On rare occasions, patients with end-stage renal disease undergoing hemodialysis may experience acute dialysis disequilibrium syndrome (DDS), or present with the more chronic disorder, dialysis encephalopathy/dementia. Symptoms may vary from mild headache, nausea and muscle cramps to more critical symptoms including myoclonus, confusion, seizures, dementia and even coma [7-9]. DDS occurs during or immediately after the procedure due to the

more rapid clearance of plasma urea compared to that in cerebrospinal fluid (CSF); thus, creating an osmotic gradient that causes water to diffuse into the brain [8]. The chronic form, dialysis encephalopathy/dementia, on the other hand, is believed to be mediated by chronic aluminum toxicity secondary to the use of aluminum-containing dialysate or aluminum-based phosphate binders [9]. There is no specific therapy for these conditions, but the rate of dialysis may be reduced, or may it be discontinued temporarily [7]. Benzodiazepines, such as clonazepam or diazepam, with anticonvulsant, antixiolytic and muscle relaxant properties have been reported to be effective in alleviating severe symptoms including myoclonus, and in preventing seizures [9, 10]. Nonetheless, prophylactic use of these drugs has not been recommended [7]. Hence, it is crucial that patients be meticulously monitored for clinical and hematological signs and symptoms that may likely indicate an adverse reaction.

In 1973, Girke et al reported that 9 of 26 patients taking clonazepam had decrease in platelet count to a minimum of 90 x 10^9/L [3]. Two years after, Veall and Hogarth also documented a case of a 52-year-old female with uncontrolled epilepsy who was initially treated with phenytoin with subsequent addition of clonazepam. The patient developed severe epistaxis and purpura nearly five weeks after starting clonazepam. Her platelet count on the day of admission was 6 x 10^9/L, which decreased even further to less than 1 x 10^9/L during the next two days. Although it was not directly stated, phenytoin and clonazepam were likely discontinued. She was given prednisone 20 mg three times per day, with gradual increase of platelet count to 48 x 10^9/L two weeks after admission, ultimately reaching normal level at five weeks from the time of admission [4]. These two reports significantly highlighted the role of clonazepam in instigating thrombocytopenia.

In addition to direct drug toxicity to blood cells and their corresponding hematopoietic precursors [1], several hypotheses and mechanisms have been illustrated in drug-induced hematologic dyscrasias, including a T-cell-mediated process [6, 11], and immune stimulation by autoantigens [12, 13], formation of hapten-induced anti-neutrophil antibody [14], and drug-dependent platelet immunoglobulin G (IgG) antibodies [15].

Studies regarding acquired aplastic anemia, a clonal stem cell disorder exemplified by peripheral blood pancytopenia with hypocellular marrow, proposed that a population of CD8-positive T cells which produce inhibitory cytokines, like tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukin-6 (IL-6), impeded hematopoiesis via mitotic cycle interference and apoptosis [6, 11]. In light of searching for possible antigens that may stimulate the immune system consequently resulting in pancytopenia, Feng et al described the possible autoantigenic role of a serum protein, diazepam-binding inhibitor related protein 1 (DRS-1). DRS-1 gene has been shown to be highly expressed in myeloid leukemia cell lines but not in monocytoid or lymphoid leukemia cell lineages. They found that high anti-DRS-1 antibody titers were present in patients with acquired aplastic anemia and myelodysplastic syndrome (MDS) displaying increased PNH type cells [12]. Takamatsu et al established that patients with acquired aplastic anemia developed antibodies to moesin, an intracellular protein that assists in microtubule formation and connects the cell membrane and cytoskeleton. The anti-moesin antibodies isolated from these patients were capable of directly inducing secretion of IFN-γ [13]. Moreover, other agents such as penicillins may act as haptens, consequently stimulating formation of antibodies against neutrophils [14].

Cases of drug-induced thrombocytopenia (DITP), with formation of drug-dependent platelet IgG antibodies have been well-documented. The two most commonly implicated drugs

are trimethoprim/sulfamethoxazole and quinine, with an estimated risk of 38 and 26 cases/10^6 users/week, respectively. It has been postulated that the sensitizing drugs possess hydrophobic and/or charged molecules that permit binding to both antibody and platelet surface [15]. Conti and Gandolfo reported two patients who were prescribed benzodiazepines, and who later developed hemorrhagic syndromes, characterized by purpura, ecchymoses and mucocutaneous bleeding with significant thrombocytopenia. The platelet counts declined to 10 x 10^9/L in patient 1, and 20 x 10^9/L in patient 2. Both patients had increased concentrations of serum platelet-associated IgG (PAIgG) antibodies and showed presence of drug-dependent platelet antibodies. Antibody cross-reactivity was also exhibited among the benzodiazepine derivatives. Of important note, patient 1 had a critical hemorrhagic crisis, with purpura, gingival bleeding, hematuria, and a significant decline in platelet count from 140 x 10^9/L to 10 x 10^9/L six hours from re-exposure to only 20 drops (5 mg) of diazepam. Discontinuation of the offending agents, with concomitant steroid therapy gradually improved their platelet counts, subsequently returning to normal values [5].

The proposed mechanisms of drug-induced hematologic dyscrasias may parallel the underlying pathogenesis prompted by exposure to clonazepam. Patients who are taking this drug must be monitored with regular CBC analyses to check for likely development of clinically significant pancytopenia. Cessation of the drug usually results in gradual improvement of blood counts. Serology may reveal presence of clonazepam-specific antibodies and may be helpful for confirmation. Once documented, it is significant to include clonazepam in the patient's drug allergy list.

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Figure Legends

Fig. 1 A. Bone marrow trephine core biopsy showing a markedly hypocellular marrow for age, with 10-20% total marrow cellularity, intermixed with adipose tissue (hematoxylin and eosin, 200x)

B. Occasional scattered erythroid and myeloid precursors, and a megakaryocyte, trephine core biopsy (hematoxylin and eosin, 400x)

Abbreviations

TNF-α: tumor necrosis factor alpha; IFN-γ: interferon gamma; IL-6: interleukin-6; CBC: complete blood count; ANA: antinuclear antibody; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; PNH: paroxysmal nocturnal hemoglobinuria; MDS: myelodysplastic syndrome; DITP: drug-induced thrombocytopenia; IgG: immunoglobulin G; PAIgG: platelet-associated IgG

Authors' contributions

MBQ, YML and CTH performed literature review, and participated in the composition of this manuscript. YML and CH obtained pertinent patient's consent, clinical data, and photomicrographs. All authors read and approve the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent

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