A 37-year-old woman was diagnosed with ovarian papillary carcinoma at the age of 14 years (currently stage IV). She has since received multiple lines of chemotherapy, including 2 lines of carboplatin in 2000 and 2008.

In 2009, during the administration of the first cycle of carboplatin (third line of treatment), she developed general malaise, fever, palmar pruritus, and severe dyspnea. The drug infusion was discontinued, symptomatic treatment was administered, and the patient immediately recovered. She tolerated a further 5 cycles of carboplatin with premedication (dexamethasone and dexamethasone and sildenaﬁl). In 2016, the patient required treatment with carboplatin because of recurrence of the disease. She received 3 red blood cell transfusions and was started on a course of levofloxacin 500 mg and methylprednisolone 250 mg. She developed an acute bilateral pulmonary thromboembolism 48 hours after administration of carboplatin and was admitted to the intensive care unit and treated with fibrinolysis. Cyclophosphamide, rituximab, intravenous immunoglobulin, and multiple transfusions of red blood cells were administered, reaching a peak hemoglobin level of 9 g/dL. On the following days, the hemoglobin dropped again to 6.5 g/dL, indicating persistent hemolysis.

Analysis of the patient’s serum revealed her ABO group to be O and her Rh type to be positive. An indirect antiglobulin test using low-ionic-strength saline yielded a negative result, confirming no underlying clinically significant alloantibodies. These initial results indicated that the patient had hemolytic anemia of immunological origin.

Drug-induced immune hemolysis was investigated to determine the drug’s involvement in the destruction of the patient’s red blood cells. Briefly, a solution of 0.88 mg/mL of carboplatin was prepared in phosphate-buffered saline at pH 7.0/7.4 (ie, same as that given to the patient). The patient’s red blood cells (RBCs) were treated with the carboplatin solution (incubated at room temperature and at 37°C for 1 hour). Hemolysis occurred only when the serum was tested with carboplatin-treated RBCs, but not with untreated RBCs (ABO group O donor), thus enabling us to conclude that the patient had carboplatin-induced immune hemolytic anemia.

The half-life of carboplatin is 167 hours (7 days), meaning that the drug would be eliminated in 7 half-lives (48 days). Given the critical situation of the patient and the unresolved hemolysis, it was decided to perform therapeutic plasma exchange (TPE) (1900 cc).

After the treatment, the patient experienced a progressive increase in hemoglobin levels, reaching a peak of 11 g/dL. She was discharged within 13 days of admission. Carboplatin is an alkylating agent that is widely used for the treatment of different types of cancer. Its main toxicity is myelosuppression, and anemia is common during treatment. Protocols for desensitization to chemotherapeutics are used to address hypersensitivity reactions. They are tailored to the patient and protect against anaphylaxis.

Drug-induced immune hemolytic anemia is a rare disease with an estimated incidence of 1 case per 1 million patients.
per year [2,3]. Exposure to a specific drug induces a rapid fall in circulating RBCs via an immune-mediated process [3]. Laboratory findings include anemia, reticulocyte elevation, hyperbilirubinemia, low haptoglobin, and elevated LDH.

The reaction reported here corresponds to a type II reaction according to the Gell and Coombs classification. Type II reactions are mediated by the interaction of preformed IgG and IgM antibodies, with antigens present on the cell surface and other tissue components. There have been 7 reported cases of carboplatin-mediated hemolytic anemia [4-10]. Interestingly, 1 publication [4] reported a similar case with a combination of a type I IgE-mediated reaction and a type II IgG-mediated reaction to carboplatin occurring during desensitization. In the present case, IgM to carboplatin was also detected and had a severe clinical course requiring TPE.

Drug-induced immune hemolytic anemia has never been reported with the administration of the first cycle. Symptoms in all cases are similar, and it seems that low back pain is characteristic. Anti-IgG and anti-C3 antibodies were found in 6 of the cases [5-9], and the patient we report was the only one who had anti-IgM antibodies. None of the previous patients received TPE, 2 died, and 5 progressed well.

TPE removes large-molecular-weight substances such as antibodies from plasma, which is extracted while a replacement solution is being infused, thus maintaining volume and oncotic pressure. This approach aims to eliminate preformed antibodies and immunocomplexes and avoid tissue damage.

Drug-induced immune hemolytic anemia is a rare condition, although it can appear in patients receiving chemotherapy under desensitization schemes. Professionals administering chemotherapy should be aware of this condition.

To our knowledge, this is the second case of immune hemolytic anemia induced by carboplatin during a desensitization protocol.

The effectiveness of TPE in the present case leads us to recommend it for patients with severe drug-induced immune hemolytic anemia.

Previous Presentations

18/05/2017: Sociedad de Madrid y Castilla la Mancha (SMCLM) de Alergología e Inmunología Clínica. Madrid, Spain. Sesión clínica interhospitalaria. Name of the case: Reacción a carboplatino: una entre un millón (Reaction to carboplatin: one in a million) by Gemma Vilá-Nadal.

27/10/2017 “Simposio Internacional Aerobiología, Contaminación y Cambio Climático”. Murcia, Spain. Oral comunicación: “Anemia hemolítica mediada por IgG e IgM con activación del complemento inducida por carboplatino en pauta de desensibilización (Hemolytic anemia IgG and IgM mediated with complement activation induced by carboplatin in a drug-desensitization program) by Gemma Vilá-Nadal.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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