Development of autoimmune hemolytic anemia during the treatment of a patient with acute myelomonocytic leukemia

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Turk J Haematol 2005;22(2): 95-99

Received: *13.07.2004* ***Accepted:*** *05.01.2005*

ABSTRACT

Drug induced autoimmune hemolytic anemia is a well-known complication of drug therapy but it is often misdiagnosed. Drug induced autoimmune hemolytic anemia is difficult to differantiate from classical autoimmune hemolytic anemia. Here, we have reported a case with autoimmune hemolytic anemia might be caused by drugs such as teicoplanin, imipenem and amphotericin B. In our case, on the fifteenth postadmission day was occur autoimmune hemolytic anemia. At this while, chemotherapy of patient had been completed and the patient have been taking antibiotherapy which include teicoplanin, imipenem and amphotericin B. Antibiotherapy could not be stopped because of febrile neutropenia. Symptoms and sings of anemia improved with prednisolon therapy. Suspicious drug must be stopped in drug induced autoimmune hemolytic anemia but in the conditions that drug could not be stopped, steroid treatment can be used in the treatment of hemolytic anemia.

Key Words: Autoimmune, Hemolytic anemia, Drug induced autoimmune hemolytic anemia.

ÖZET

Akut miyelomonositik lösemili bir hastanın tedavisi sırasında ortaya çıkan otoimmün hemolitik anemi

İlaca bağlı otoimmün hemolitik anemi, ilaç tedavisinin iyi bilinen bir komplikasyonudur fakat sıklıkla yanlış tanı konulur. İlaca bağlı otoimmün hemolitik anemiyi klasik otoimmün hemolitik anemiden ayırmak zordur. Biz, burada; teikoplanin, imipenem, amfoterisin B gibi ilaçların neden olabildiği otoimmün hemolitik anemili bir olgu sunmaktayız. Olgumuzda; kabul sonrası 15. günde otoimmün hemolitik anemi gelişti. Bu sırada hastanın kemoterapisi tamamlanmıştı ve hasta teikoplanini imipenem ve amfoterisin B'yi içeren antibiyotik tedavisi almaktaydı. Febril nötropeni nedeni ile antibiyotik tedavisi kesilemedi. Aneminin semptom ve bulguları prednizolon tedavisi ile düzeldi. İlaca bağlı otoimmün hemolitik anemide, şüpheli ilaç kesilmelidir fakat ilacın kesilemediği durumlarda steroid tedavisi hemolitik aneminin tedavisinde kullanılabilir.

Anahtar Kelimeler: Otoimmünite, Hemolitik anemi, İlaca bağlı otoimmün hemolitik anemi.

INTRODUCTION

Haemolysis is a process characterized by accelerated red cell destruction, which can be compensated for if the body steps up production of new red blood cells. However, if red blood cell destruction surpasses production, haemolytic anemia can result. Haemolytic anaemia is traditionally categorized by cause as either congenital or acquired[1]. The term "acquired haemolytic anaemia" was first coined in the early 1900's and its now commonly used to describe haemolytic anaemia triggered by extrinsic factors such as immune disorders, drugs, infections, mechanical trauma to red cells, exposure to toxins and other miscellaneous causes[1]. Autoimmune haemolytic anaemia (AIHA) may be classified in two complementary ways. Autoimmune haemolytic anaemia is mediated by warm reactive autoantibodies and/or cold reactive autoantibodies. It is also useful to classify AIHA based on the precense or absence of underlying disease. When no recognizable underlying disease is present, the AIHA is termed primary or idiopathic. When AIHA appears to be a manifestation or complication of underlying disorders, the term secondary AIHA is applied. Lymphocytic malignancies, particularly chronic lymphocytic leukaemia and lymphomas, account for about half of the secondary AIHA cases. Other associated diseases are rheumatic disorders (e.g. SLE), certain infections (e.g. infectious mononucleosis, *Mycoplasma pneumoniae* infections), nonlymphoid neoplasm (e.g. ovarian tumors), chronic inflamatory diseases (e.g. ulcerative colitis), ingestion of certain drugs (e.g. α-methyldopa)[2]. AIHA has rarely been reported in other haematological malignancies such as myelodysplastic or myeloproliferative syndromes[3]. We reported a case of clinically relevant, drug induced severe autoimmune haemolysis due to IgG warm antibodies developed during the treatment of a patient with acute myelomonocytic leukaemia.

CASE REPORT

A 43-years old man was admitted to our clinic because of bicytopenia and monocytosis. The patient complained about progressive weakness, lack of appetite for three months and hyperthrophy of his gums for a year. His past medical history did not reveal any special feature or operation. He took no other medication or illicit drugs.

On physical examination, he presented with hyperthrophied gum, pale skin and mucosa. He had multiple microlymphadenophaties in his cervical, axillar and inguinal region. Red papuller lesions were noted on the skin. There was no hepatosplenomegaly in his physical examination. His haematological profile revealed white blood cell count 21.5 x 10^9/L, monocyte count 17.2 x 10^9/L (peripheric smear: neutrophils 6%, lymphocytes 8%, eosinophils 2%, blast 5% and other cells were monocytes and promonocytes 79%), Hb 6.81 g/dL, Hct 18.1% and platelet count 44.4 x 10^9/L. The reticulocyte count was 0.95% and the ESR: 120 mm/h. Biochemical tests revealed on elevated LDH. 51% of nonerythroid cells in the bone marrow aspiration specimen were consisted of monoblasts, promonocytes and monocytes and 26% of nonerythroid cells were consisted of myeloblasts and promyelocytes (Figure 1). Megakaryocytes and erythroid cells were decreased in the

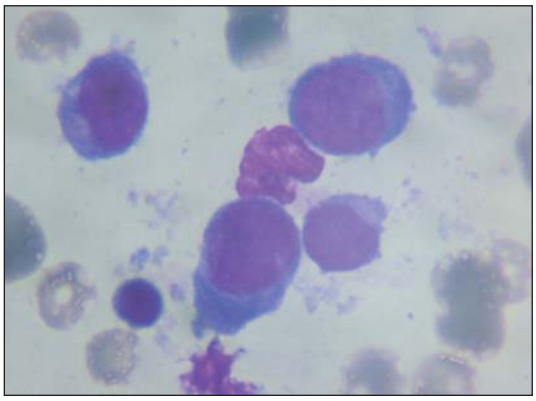

Figure 1. Bone marrow aspiration.

examination of the specimen. The bone marrow biopsy showed hypercellularity, with infiltration by CD15 and MPO positive (5-10%) and CD68 positive (60%) immature cells, depressed erythropoiesis and decreased number of megakaryocytes. At the light of these finding, the patient was diagnosed as acute myelomonocytic leukaemia. The skin biopsy was performed and pathological investigation showed leukaemic infiltration.

Treatment of the patient was initiated with chemotherapeutic agents. The patient started treatment with chemotherapy consisting of idarubicin (45 mg/m^2,1-3 days) and cytarabine (100 mg/m^2,1-7 days). Neutropenia became more severe at the fifth day his chemotherapy and fever was detected. Therefore; febrile neutropenia protocol which include piperacillin/tazobactam 4.5 g (qid) and amikacin 1000 mg once a day was started. Teicoplanin was added at the fourth day of his antibiotherapy and amphotericin-B (lipo) 2 mg/kg was added at the eighth day of his antibiotherapy. At the thirteenth day of his antibiotherapy, piperacillin/tazobactam and amikacin was stopped and imipenem was added due to possible anaerobic infection in his gums. There was no isolation any agent at the blood and other culture during these period.

Hb level rapidly decreased on the fifteenth day of his antibiotherapy and the patient presented symptoms and signs of severe anaemia. Features of a haemolytic anaemia were observed (Hb level: 5.5 g/dL, total bilirubin: 7.6 mg/dL, indirect bilirubin: 3.4 mg/dL, LDH level was 1187 U/L) and absolute reticulocyte count: 22 x 10^9/L; 0.75% reticulocyte. An IgG spesific direct antiglobulin test (Coombs) was positive (Table 1). A cold agglutinin test was negative. Thus, we decided that the patient had autoimmune haemolytic anaemia. Despite difficulties in cross-matching, transfusion therapy with the least imcompatible blood unite available was performed. Prednisolon therapy with a dose of 48 mg/day was started to the patient then, the dose was increased to 96 mg/day in eighth of his therapy. Hb level was increased slowly with prednisolon therapy. After two weeks, prednisolon therapy was gradually tapered and than it was stopped.

DISCUSSION

Classifications of autoimmune haemolytic anaemia include warm autoimmune hemolytic anaemia, cold agglutinine syndrome, paroxysmal cold hemoglobinuria, mixed type autoimmune haemolytic anaemia and drug induced immune haemolytic anaemia. Each of these causes except for drug induced immune haemolytic anaemia was divided into two category labelled as idiopathic or secondary[4]. Autoimmune haemolytic anaemia have been reported as a rare manifestations of acute myelogenous leukaemia. Seven similar cases were detected in the literature as case reports or letters. Deutsch M et al reported autoimmune haemolytic anaemia in a patient with acute myeloblastic leukaemia and there was an improvement in haemoglobine level and lowering of RBC-associated

Table 1. Some data of the patient

Admission day	Hb level (g/dL)	Total bilirubin (mg/dL)	Indirect bilirubin (mg/dL)	LDH level (U/L)	Ret. (%)	DAT
1st day	6.81	0.50	0.18	288	0.95	
5th day	7.56	0.93	0.50	220	-	
10th day	6.76	1.09	0.42	-	-	
20th day	5.5	7.6	3.4	1187	0.75	(+)
40th day	8.5	0.5	0.2	356		(+)

IgG titer was observed during chemotherapy[5]. Anecdotal reports revealed the possibility of positive direct antiglobulin test in cases of acute leukaemia. But only a few cases of frank autoimmune haemolysis in de novo acute myeloblastic leukaemia have been reported until now[5-7].

Although drug induced immune haemolytic anaemia is a well-known complication of drug therapy (frequently induced by methyldopa, penicillin, cephalosporin, diclophenac, procainamid), it is often misdiagnosed due to an inconclusive patient history and/or serological work-up[8]. A few publication have been found about the drugs used that can cause haemolytic anaemia in treatment of febril neutropenia. One of these was associated with teicoplanin in which it was used to for a superficial sternal wound infection after coronary artery bypass grafting[9]. In a patient who was treated with piperacillin/tazobactam due to pneumonia possibly caused haemolysis and it was the first reported case of haemolytic anaemia associated with tazobactam[10]. Last of these reports was associated with amphotericin-B. Salama A et al reported an eight-years-old boy who developed acute intravascular haemolysis following therapy with amphotericin B[11].

In our case; there was no autoimmune haemolytic anaemia at beginning of the disease. For this reason; we did not consider de novo autoimmune haemolytic anaemia associated with acute myelomonocytic leukaemia. In case, on the fifteenth day of his antibiotherapy was occur autoimmune haemolytic anaemia. At this while, chemotherapy of patient had been completed and the patient have been taking antibiotherapy which include teicoplanin, imipenem and amphotericin B. Piperacillin/tazobactam and amikacin had been stopped when autoimmune haemolytic anaemia was detected.

Antibiotherapy could not be stopped because the patient had neutropenic fever. Although the patient was continue to use antibiotherapy which was include teicoplanin, imipenem and amphotericin, Hb level was gradually increase, bilirubin and LDH levels were decrease, symptoms and sings of anemia improved after prednisolon therapy was started. The reticulocyte count which was low beginning of the disease was also detected low during the haemolytic anaemia course. Low reticulocyte count might be due to bone marrow supression by chemotherapy which include idarubicin and cytarabine.

Drug induced immune haemolytic anaemia can occur due to various drugs those were used in the treatment of diseases. In our case, antibiotics those were used for febril neutropenia may be the cause of drug induced immune haemolytic anaemia. In the state of drug induced immune haemolytic anaemia, suspicious drug must be stopped. Because of the conditions that we could not be able to cease the drug, steroid treatment can be used in the treatment of haemolytic anaemia.

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