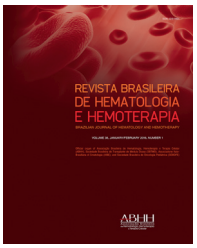
Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
www.rbhh.org



Case Report

A closer look into blood group discrepancy arising due to an underlying malignancy

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ARTICLE INFO

Article history:
Received 20 February 2016
Accepted 11 April 2016
Available online 2 May 2016

Introduction

The ABH antigens are histo-blood group antigens that are present in circulating blood cells, tissues and body fluids. The association of blood groups with various disease states has been well documented in the literature. Both hematopoietic and non-hematopoietic malignancies are associated with blood group changes. In solid organ malignancies, excessive blood group substances produced by the tumor lead to blood group discrepancies.[1] However, such discrepancies are rare with a very few case reports in the literature. Herein, we describe an unusual case of a blood group discrepancy in a 48-year-old lady who was diagnosed with signet ring cell gastric adenocarcinoma.

Case description

A blood sample of a 48-year-old lady was received for blood grouping and cross-matching. Her hemoglobin, total leukocyte and platelet counts were 5.6 g/dL, 4800 cells/μL and 3.84×10^5 cells/μL, respectively. As per our protocol, we did the preliminary blood grouping of the patient with unwashed cells using the tube technique to check availability of blood in our inventory. Forward grouping results were as follows: no agglutination with anti-A and anti-B antisera and, weak agglutination with anti-A,B monoclonal antiserum. Reverse grouping revealed A group. The results were similar with a repeat sample and column agglutination technology. Reaction with anti-A1 lectin was negative and reaction with anti-H lectin was 4+. The initial blood grouping was mimicking the Ax phenotype. As per her previous blood group records, she was A Rh D positive. The patient had a history of transfusion five years previously during a hysterectomy. The blood grouping was repeated after washing her red cells thrice with physiological saline (0.9%) as per the departmental standard operating procedure. Strong agglutination was noted with anti-A and anti-A,B (Figure 1). Reaction with anti-A1 lectin was positive and reaction with anti-H lectin was 4+. Hence, her blood group was confirmed as A1 Rh D positive. Saliva secretor status was also studied. She was a secretor of both A and H blood group substances.

Meanwhile, we gathered details of the patient's medical history. The patient was admitted two months previously

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http://dx.doi.org/10.1016/j.bjhh.2016.04.007

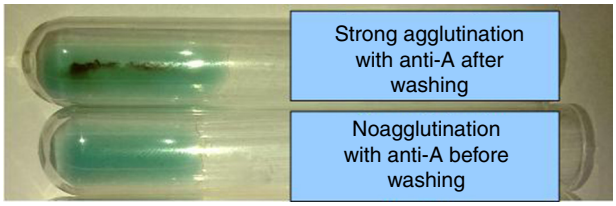

Figure 1 – Unwashed red cells of the patient showed no agglutination with monoclonal anti-A, while after washing three times, red cells showed strong agglutination with anti-A.

with a history of abdominal pain. Multislice spiral computed tomography (CT) of the abdomen revealed a heterogeneously enhanced transmural wall thickening (3.5 cm) with a large ulcer and irregular mucosa in the gastric fundus and body. The mass was invading the left adrenal gland. There was no associated lymphadenopathy or distant metastasis. These findings were consistent with a diagnosis of locally advanced gastric cancer. Upper gastrointestinal endoscopic biopsy confirmed the diagnosis of a primary gastric signet ring cell carcinoma. She completed two cycles of 5-flurorouracil and cisplatin-based palliative chemotherapy. The present blood sample was taken three weeks after the second cycle of chemotherapy.

We suspected that there might be A blood group substance in the patient's serum which inhibited the reaction with anti-A antiserum. The amount of inhibiting substance in the patient's serum was tested based on the methodology described by Treacy et al.[2] Monoclonal anti-A was titrated against A2 cells. The titer of anti-A was 1:512 and a dilution of 1:16 was used for the study (the next to the last dilution showing a 4+ reaction with A2 cells was used). A2 cells were prepared from a single donor. Doubling dilutions of serum (each tube containing 100 μL of the patient and a healthy blood group A donor) was made and 100 μL of diluted monoclonal anti-A was added to each tube. The suspensions were mixed well and incubated for 30 min at room temperature. An aliquot of 100 μL of washed A red cells was added to all tubes, incubated at room temperature for 30 min and centrifuged at 1000 rpm for 1 min. Complete neutralization (inhibition of hemagglutination) was seen up to 1:64 dilution of the patient's serum, while normal control serum showed no inhibition. Hence, it was concluded that the blood group discrepancy noted in this patient was due to the presence of an excess of A blood group substance in her serum, probably secreted by the tumor cells. The patient was transfused with one unit of A1 Rh D positive packed red blood cells and the transfusion was uneventful. Her post-transfusion hemoglobin was 7 g/dL. She was followed-up for three weeks after chemotherapy. There was no apparent reduction in neutralization activity of the serum.

Discussion

Several studies in the past have reported on malignancies and their effects on blood groups. Other than red cells, specific substances of ABH blood groups have been detected in mucous glands, epithelial cells, neurons, and vascular endothelial cells.[3,4] Alterations of red cell antigens occur with both hematologic and solid malignancies. In hematological malignancies, loss/weakening of red cell antigen expression occurs due to genetic and epigenetic changes in the A and B transferase genes. In solid tumors (bladder, lung, head and neck, cervical, and thyroid), loss of expression of the histo-blood group ABH antigens from tumor cells is a known event, but red cell antigen expression may not be reduced.[5] Rather, neutralization of typing antiserum by the blood group-specific soluble substances secreted by tumor cells can be seen.[1] The first report of such association was in 1959 when Barber and Dunsford reported excess of blood group A substance in a female patient with gastric carcinoma resulting in a blood group discrepancy.[6] This finding has also been reported to occur in pancreatic, ovarian, colonic, and bile duct carcinoma and, pseudomucinous ovarian cysts.[1,7,8] Secretions from tumor cells enter the blood stream either directly or through ascitic fluid absorption.[8] Saeed and Fine demonstrated excess A and H blood group substances in tumor cell cytoplasm by immunofluorescence studies in a patient with stomach adenocarcinoma. These excess soluble antigens probably neutralized anti-A antiserum that led to ambiguous blood grouping.[9] Rouger et al. studied 70 patients with gastric or colon carcinoma and concluded that the individuals of blood group A had higher levels of A blood group substance in serum when compared to controls,[10] however the reason for this biochemical behavior is not known. Joshi et al. from India reported a case of blood group discrepancy due to excess secretions of A blood group substance by ovarian mucinous cystadenoma. After resection of the tumor, the discrepancy was reversed.[11] Unusually, blood group substances have been found in healthy individuals and even at lower concentrations in newborns.[6,8,9]

ABH blood group substances neutralize the commercial antiserum providing no binding site for red cell antigens. Complete washing of red cells removes the inhibiting substance unmasking the effect. In our case, complete inhibition was seen up to 1:64 dilution of the patient's serum. In a series of four patients, Treacy et al. noted high concentrations of A blood group substance in serum with titers ranging from 1:512 to 1:2048, whereas Joshi et al. reported hemagglutination inhibiting activity of A blood group substance only up to a 1:128 dilution.[2,10]

Loss of ABH antigens from the dedifferentiated tumor cells is also known and has been associated with a negative prognostic impact. It is evident from the literature that most of the patients with carcinoma who were reported to have this neutralization effect in serum were diagnosed with end stage/advanced disease and later succumbed to the disease.[2,6,9] Although this statement seems quite simple, some questions still remain unanswered. (1) Is excess of blood group substances in serum related to tumor clinical behavior and prognosis? (2) Is the finding of excess blood group substances more common in adenocarcinomas of the gastrointestinal tract and ovaries than tumors at other sites? Further exploration is needed to comment on these questions. Notwithstanding, rapidly expanding molecular diagnostics, serological methods undoubtedly have a first-line role to solve blood group discrepancies in the practice of transfusion medicine.

We conclude that excess blood group substances in the serum neutralizing the typing antiserum is a very rare phenomenon. This has been demonstrated in patients with gastrointestinal tract carcinoma and ovarian cysts. Serological techniques would be helpful in resolving these blood group discrepancies where molecular methods are unavailable especially in resource-limited settings.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank Dr Karishma for assisting us in writing the manuscript.

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