JMS 2022;5 (2):76-78
UDC:616.72-002.77-06:616.155.194.17
DOI: 10.55302/JMS2252076s

CORRELATION BETWEEN RHEUMATIC DISEASE AND AUTO HEMOLITIC ANEMIA

Dejan Spasovski[1,3], Emilija Sandevska[1,3], Svetlana Krsetvska-Balkanov[2,3], Aleksandra Pivkova-Veljanovska[2,3]
[1]University Clinic for Rheumatology, [2]University Clinic of Hematology, Clinical Center Mother Therese, Skopje, Republic of North Macedonia,
[3]Faculty of Medicine, Ss Cyril and Methodius University in Skopje, Republic of North Macedonia

Abstract

The autoimmune hemolytic anemias antibody can be hot or cold, have an incidence of 70 to 80% may be idiopathic in 50 to 60% and the rest of the cases secondary to lymphoproliferative disorders, collagen disease, drugs, solid tumors, infections and inflammatory bowel disease.

RA may result in the reduced lifespan of red blood cells. This could lead to anemia if the body is unable to produce new red blood cells at a sufficient rate. Understanding these links between RA and anemia is crucial.

Anemia is a common comorbidity in individuals with rheumatoid arthritis (RA). In fact, anemia of the type characterized by low serum iron concentrations in conjunction with adequate iron stores is frequently associated with RA and has served as a model for anemia of chronic disease. Rheumatoid vasculitis can affect blood vessels in many parts of your body. For this reason, it can cause many different symptoms.

It most often damages blood vessels to the skin, fingers and toes, nerves, eyes, and heart. This reduces blood flow to these areas and damages them.

Rheumatoid arthritis (RA) may be associated with a range of extraarticular manifestations, with hematologic complications including anemia and other conditions with hematologic abnormalities, such as Felty syndrome and lymphoproliferative disorders, particularly lymphoma and large granular lymphocyte (LGL) leukemia.

Keywords: rheumathic disease, autohemolitic anemia.

Introduction

There are hemolytic anemias of different origin. For instance, these states may be induced by means of some exogenic hemolytic factors: by different organic and unorganic hemolytic toxins (phosphorus, phenylhydrazin, saponins, arsenicum, lead and biotoxins – snake venom, mushroom poisons, mycotoxins, etc.), some medical preparations, radiations, some infectious agents and haevy burns. Besides, in some cases, hemolytic anemias are induced by antibodies and immunocompetent cells against own tissues (autoimmune hemolytic anemia).

Reason of immunization of autoimmune hemolytic anemias may be some infection diseases (malaria, grippe, pneumonias, i.e. viruses, bacteria, acute anaerobic or streptococcal sepsis, mycoplasma pneumoniae,) and some chemical and physical factors and influences.

There is a relationship between B-cell oncogenesis and autoimmunity disease.

According to clinical studies malignant tumors in autoimmune hemolytic anemias appear in 45-47%. Observation of a large body of literature, permit to suggest that quite frequently tumor cells in autoimmune hemolytic anemias have lymphoid and macrophagal nature.

The analysis of 234 patients with autoimmune hemolytic anemias showed chronic lympholeukemias, malignant lymphomas, multiple myelomas, alimentary tract cancers and so on [1].

The analysis of 168 patients with hemolytic anemias showed approximately similar results [2].

The incidence of tumors of this localization and histogenesis increases significantly during such human autoimmune diseases as systemic lupus erythematosus, rhematoid arthritis, etc. [3-5].

Some viruses, like grippe, rubella, HIV, and some carcinogenic agents can induce fussion and at the soma time cytolitic effect in somatic cell[6,7].

For instance, toxin of *Aspergillus flavus* – aflatoxin, together with heavy toxic action, induces malignant tumors (hepatomas) of the liver. Such different effects of these agents on somatic cells possibly depend on the size of plasma membranes' pores induced by them.

For instance, high doses of carcinogenic agents lead to partial increasing of quantity of giant polynuclear cells, but further increase of this dose induces massive cellular lysis. In low doses of carcinogenic agents, dikaryons (cells, with comparatively high oncogenic potency) are observed most frequently.

Larger perforations induce considerable destruction of cell membranes and following cytolysis together with the perishing of these cells [8].

There are some assumptions about the association of *Vipera lebetina* bites with the development of cancer of different localization and histogenesis. For instance, after bite of snake with hemolytic action of venom (*Vipera lebetina, Vipera Russellii,* etc.) together with massive destruction of erythrocytes hemolysis. Some Fungus toxins, like *Aspergillus ochraceus, Aspergillus flavus, Penicillium islandicum,*may give some similar action.

In our opinion, the mechanism of malignant transformation in autoimmune reactions can be based on the inclusion of immunocompetent cells in different cellular cooperations, which is their normal physiological property.

As it is shown, in case of autoimmune hemolytic anemia or allotransplantations, the macro organism reacts to the modificated (foreign) cells by development of humoral and cellular immune responses (immune cytolysis).

In the development of cytolysis the most important roles are played by specific antibodies and T-killer (cytotoxic) cells (immune effectors). 1. Antibody molecules have 2 main functions: they bind to the immunogenic antigens and after interaction with these antigens, initiates involvement of different cells and molecules. The constant region (C region) of the antibodies defines the type of the response after the antibody-antigen interaction, whether this is complement-mediated lysis, cellular cytotoxicity, enhanced phagocytosis, etc. 2. The cell-immune cytolysis is carried out directly by the killers (T-cytotoxic cells). The cytotoxic effect of these cells is realized in the target cells plasmalemma by special proteins – perforins which lead to the formation in this organoid**.** This cells generate substances of cytotoxic and cytolytic action, causing thus cell necrosis with disintegration of its plasmalemma or induction of apoptosis. Perforins (together with granzymes and granulolyzins) are localized in killer cells (macrophages, T-lymphocytes, NK-cells) granules. In the presence of calcium, perforines interact with the plasmatic membrane of the target cells and after the polymerization they are forming the transmembrane channels (pores) in this organoid. In the case of great number or size, these pores induce the cells destruction or other cytopathogenic effects. So both, cytotoxic cells and antibodies can induce damages of some degree plasma membranes in somatic cell. This condition can represent as precancerous state and later the true cancerous cells formation [9,10].

Target cell killing is carried out in several phases: 1) contact with killer-target-cell; 2) activation on killer cell; 3) killer cell make exocytosis of this toxic substances; and 4) toxic effect directed on target cell. Thus, pore-forming enzyme, antibodies, peptids, etc. cause plasma membrane damage in target cells, with consequences as diverse as proliferation or cell destruction.

Supposing that leucocytes (in this concrete case, lymphocytes and macrophages) are phenotypically dominant cells, their fusion with each other and with other somatic cells may lead to tumor formation of lymphoid and macrophagal nature.

Carcinogenic agents and even infectious viruses and bacterial membranotoxins may induce both fusion and hemolytic effects in somatic cells simultaneously. In autoimmune hemolytic anemias side by side with hemolysis it may take place process of somatic cells fusion with further formation of tumor cells. [11-15].

Thus, cell fusion may in some cases of autoimmune process produce a cell with tumor properties. Carcinogenic agents or some other reasons (immunocompetent cells, antibodies) may create the autoimmunization background in a macro organism, which may lead to multiple intercellular contacts between immunocompetent cells and cells with aberrant antigens. In case of cells fusion, initiation of malignant neoplasms of lymphoid or macrophagal histogenesis is expected to take place.

As a possible cellular mechanism of malignization in hemolytic anemias of different origin is proces of fusion of immunocompetent cell with other ones.

All the more that, formation of hybrid cells in vivo, it is possible consider as an physiological phenomenon.

REFERENCES

1. Batailler, ER; Klein, B; Durie, BGM. et al. Interrelationship between autoimmunity and B-lymphoid cell oncogenesis in humans. Clin. Exp. Rheumatol. 1989; 7:319-328.
2. Lechner, K; Obermeier, HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore). 2012; 91:195-205.
3. Bernatsky, S; Ramsey-Goldman, R; Rajan, R. et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. Ann. Rheumatol. Dis. 2005; 64 :1507-1509.
4. Bernatsky, S; Ramsey-Goldman, R; Clarke, AE. Malignancy in systemic lupus erythematosus: what have we learned ? Best Pract. Res. Clin. Rheumatol. 2009; 23 (4) :539-547.
5. Landgren, AM; Landgren, O; Gridley, G. et al. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4,5 million US male veterans. Cancer, 2011; 117 (6) :1163-1171.
6. Vaananen, P; Kaarianen, L. Fusion and hemolysis of erythrocytes caused by three togaviruses: Semliki Forest, Sindbis and Rubella. J. Gen. Virol. 1980; 46:467-475.
7. Huang, RT; Rott, R; Klenk, HD. Influenza viruses cause hemolysis and fusion of cells. Virology. 1981; 110:243-247.
8. Gogichadze, GK; Misabishvili, EV; Gogichadze, TG. Tumor cells formation by normal soma- tic cells' fusion and cancer prevention prospects. Med. Hypotheses. 2006, 66, 1 :133- 136.
9. Gogichadze, GK; Gogichadze, TG. Karyogamic theory of cancer cell formation from the view of the XXI century. Nova Biomedical Books, New York. 2010.
10. Gogichadze, GK; Gogichadze, TG; Kamkamidze, GK. Presumably common trigger mechanism of action of diametrically different carcinogens on target cells. Cancer and Oncology Research. 2013; 1 (2), 65-68.
11. Chen YF, Xu SQ, Xu YC, Li WJ, Chen KM, Cai J, Li M. Inflammatory anemia may be an indicator for predicting disease activity and structural damage in Chinese patients with rheumatoid arthritis.Clin Rheumatol. 2020 Jun;39(6):1737-1745.
12. Weerasinghe S, Karunathilake P, Ralapanawa U, Jayalath T, Abeygunawardena S, Rathnayaka M.J.Pure red cell aplasia secondary to rheumatoid arthritis: a case report. Med Case Rep. 2021 Dec 6;15(1):578.
13. A.Espinosa-Orantes, M. A. Hernandez-Vera, J. D. Juarez-Villa, G.E, A. Guadalupe, and G. Flores. Rheumatoid Arthritis and Autoimmune Hemolytic Anemia as First Manifestation of Rhupus. Case Rep Rheumatol. 2020; 2020: 8870643.
14. Nikiphorou E, de Lusignan S, Mallen C, Khavandi K, Roberts J, Buckley CD, Galloway J, Raza K.Rheumatology (Oxford). Haematological abnormalities in new-onset rheumatoid arthritis and risk of common infections: a population-based study.2020;59(5):997-1005.
15. Muñoz AM, Orozco Niño JA, Seehaus CM, Giménez Conca AD, Chuliber FA, Lo Giudice LF, Bendek. Evans syndrome and rheumatoid arthritis as autoimmune manifestations of large granular T-cell leukemia. GE.Medicina (B Aires). 2021;81(6):1060-1064.