Acquired haemolytic anaemias

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The acquired haemolytic anaemias are usually divided into **two main** categories, depending on the mechanism by which the premature destruction of red blood cells is produced.

1-The **immune haemolytic** anaemias, antibodies are the main agents of destruction

2-The **non-immune acquired haemolytic**

anaemias result from diverse causes and mechanisms of haemolysis.

Immune haemolytic anaemias

Antibody-mediated haemolysis is an important cause of acquired haemolytic Anaemia.

Typically, the immune haemolytic anaemias are distinguished from the non immune by detecting antibody on the surface of red cells by the direct antiglobulin test (DAT), also known as the Coombs test.

Classification of immune haemolytic anaemia

Antigen type	Antibody	Diseases	Associations
Autoimmune	Warm antibody	Primary	Idiopathic
		Secondary	Autoimmune diseases (ITP, SLE, Rheumatoid arthritis)
			Lymphoproliferative disorders
			Infections (EBV)
			Ovarian cysts
			Ovarian carcinoma and some other cancers
			Drugs
	Cold antibody	Cold haemagglutinin disease (CHAD)	
		Cold antibody syndromes	Infections (*M. pneumoniae*), lymphoproliferative disorders
	Donath–Landsteiner antibody	Paroxysmal cold haemoglobinuria (PCH)	Post viral, syphilis
Alloimmune	Induced by red cell antigens	Haemolytic transfusion reactions	
		Haemolytic disease of the newborn (HDN)	
		Post-stem-cell allografts	
	Drug dependent	Antibody/macrophage mediated	
		Antibody/complement mediated	
		Membrane modification	
		Autoimmune	

Autoimmune haemolytic anaemias

Autoimmune haemolytic anaemias (AIHAs) are caused by antibody production by the body against its own red cells.

They are characterized by a positive direct antiglobulin test (DAT), (Coombs' test).

-'warm' and 'cold' types according to whether the antibody reacts more strongly with red cells at 37°C or 4°C.

Warm autoimmune haemolytic anaemias

The red cells are coated with **immunoglobulin (Ig), usually immunoglobulin G (IgG) alone or with complement,** and are therefore taken up by RE macrophages which have receptors for the Ig Fc fragment.

Part of the coated membrane is lost so the cell becomes progressively more spherical to maintain the same volume and is ultimately prematurely destroyed, predominantly in the **spleen.**

***When the cells are coated with IgG and complement or complement alone, red cell destruction occurs more generally in the RE system**

The disease may occur at any age, in either sex, and presents as a haemolytic anaemia of varying severity .

Presentation is variable and depends on the speed with which anaemia develops, the capacity of the bone marrow to compensate and the effects of any associated disease

Typically, the onset is insidious, with gradual awareness of symptoms of anaemia or observation of pallor or mild icterus by friends or relatives.

Occasionally, the onset is acute, with rapidly developing anaemia and, in older patients, the risk of heart failure.

Rarely, severe fulminating haemolysis may occur, resulting in life-threatening anaemia.

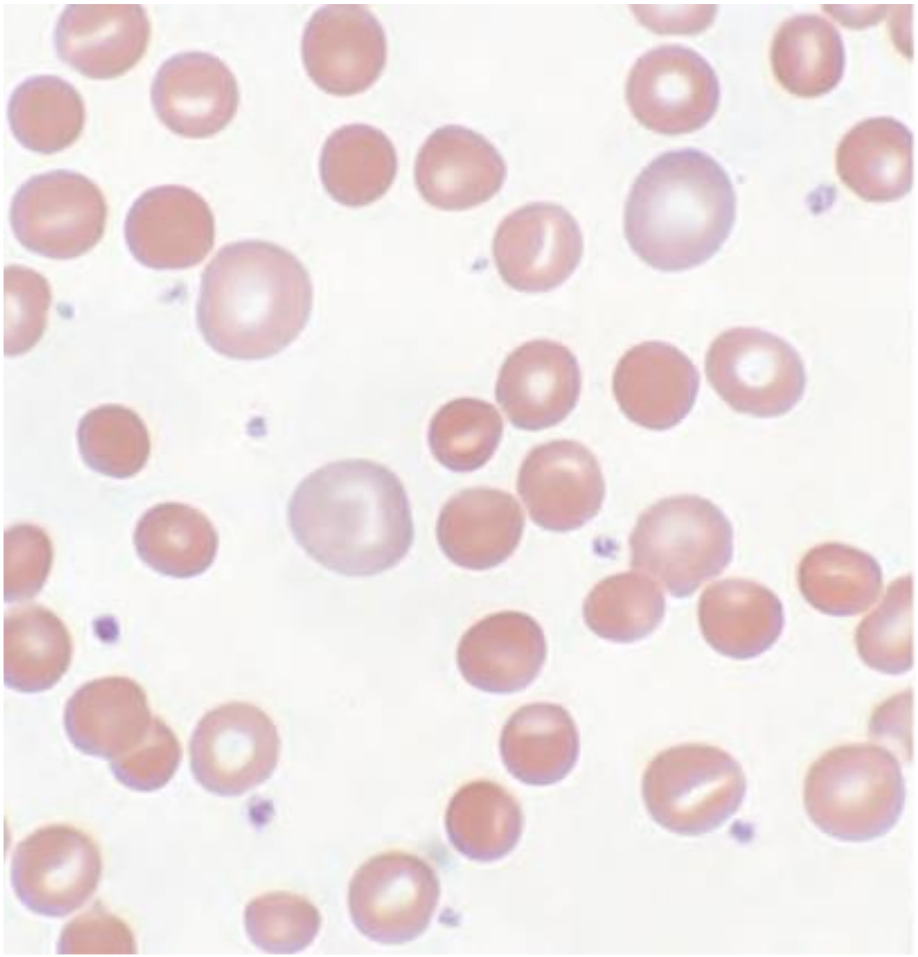
- The spleen is often enlarged.
- The disease tends to remit and relapse .

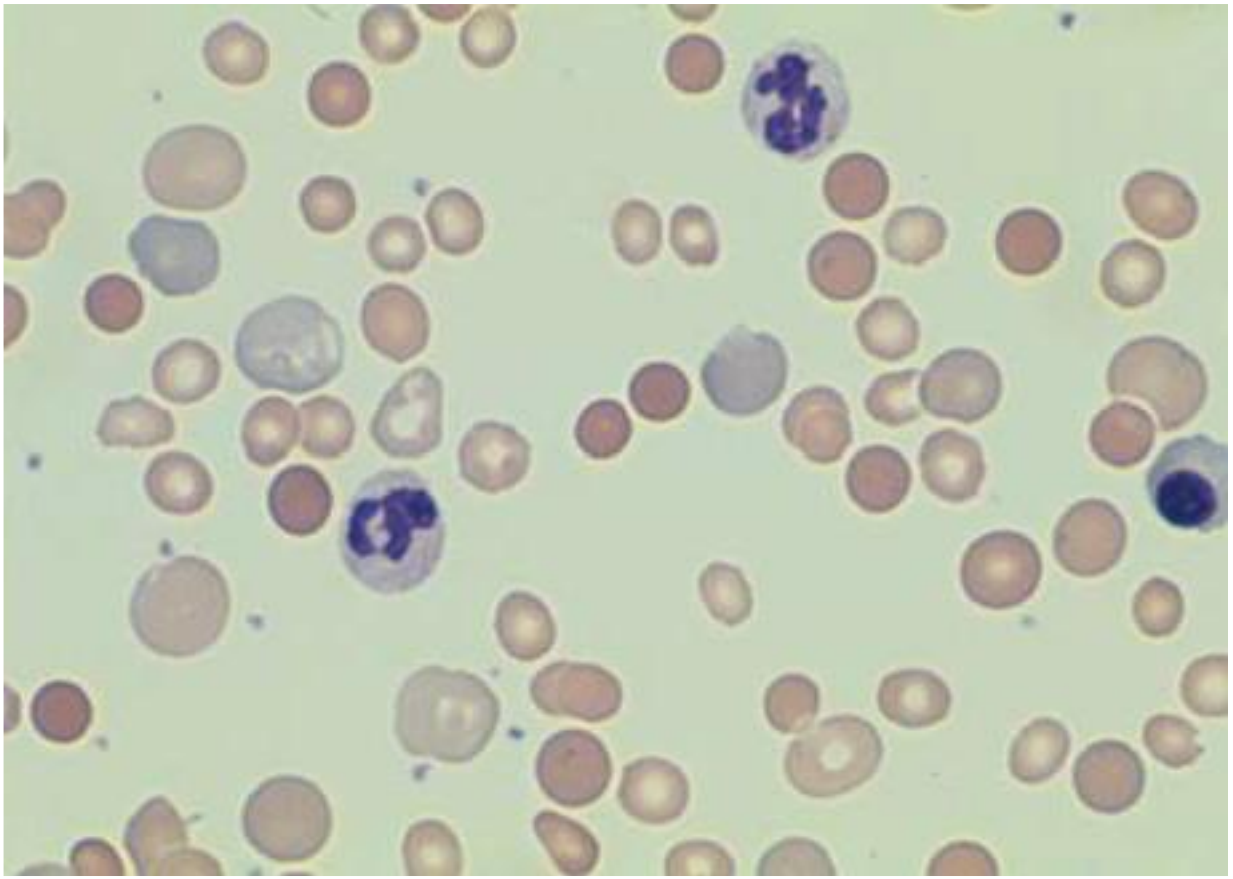
Laboratory findings:

-Anaemia with marked reticulocytosis is present .

-The peripheral blood film is characterized by polychromasia, spherocytes and circulating nucleated red cells

Blood film in warm autoimmune haemolytic anaemia. Numerous microspherocytes are present and larger polychromatic cells (reticulocytes).





- The DAT is positive as a result of IgG, IgG and complement or IgA on the cells .
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-Autoantibody in the serum may show specificity within the Rh system (e.g. autoanti-e), but in most cases is pan-reactive with all red blood cells.

-The autoantibody reacts at 37°C. In very rare cases, the amount of antibody remaining on the red cell surface is insufficient to be detected by the conventional DAT..

It may occur alone,Idiopathic , or in association with other diseases .

When associated with idiopathic thrombocytopenic purpura (ITP), a similar condition affecting platelets ,it is called Evans' syndrome.

When secondary to systemic lupus erythematosus, the cells typically are coated with immunoglobulin and complement.

Idiopathic warmAIHA

- Idiopathic warm AIHA with no underlying cause or associated disorder accounts for approximately 30% of patients with a.DATpositive haemolytic anaemia.

There is a male preponderance in the childhood setting in contrast to females in adult cases.

In girls, AIHA may precede clinical or immunological evidence of SLE which should not be excluded on account of initial negative serology.

Evans syndrome

Evans syndrome is defined as **the combination of AIHA and immune thrombocytopenia (ITP) .**

The onset of thrombocytopenia may *coincide* with haemolysis or may arise *separately*. The platelet and red cell antibodies are distinct and do not cross-react.

Lymphoproliferative diseases

Lymphoproliferative diseases, including B-cell chronic lymphocytic leukaemia (CLL), low-grade B-cell non-Hodgkin lymphoma and Hodgkin lymphoma are well described in association with cases of warm AIHA.

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The AIHA may **precede** the diagnosis of lymphoma by months or years, may occur **simultaneously** with onset of the LPD or occur **afterwards.**

Antibody response is thought to be due to **immune dysregulation** rather than direct production by the malignant clone. Antibodies are polyclonal and have no distinct pattern of type or specificity.

Drug-related warmAIHA

Drug-related warm AIHA caused by antibodies directed against self-antigens has been reported in the literature over many years including agents such as **mefenamic acid, levodopa , procainamide and fludarabine .**

Cold autoimmune haemolytic anaemias

In these syndromes the IgM autoantibody attaches to red cells mainly in the peripheral circulation where the blood temperature is cooled

The autoantibody may be **monoclonal, as in primary cold haemagglutinin syndrome** or **associated with lymphoproliferative disorders**, or may be **a transient polyclonal response following infections such as infectious mononucleosis or *Mycoplasma* pneumonia**..

The IgM antibodies which bind to red cells optimally at 4°C, are highly efficient at fixing complement such that intravascular and extravascular haemolysis can occur.

Only complement factors can be detected on red cells in laboratory tests as the IgM antibody is eluted off as cells flow through warmer parts of the circulation

The antibody is directed against the **‘I’** antigen on the red cell surface in nearly all these cold AIHA syndromes. In infectious mononucleosis it is **anti-i.**

Idiopathic cold haemagglutinin disease

Idiopathic cold haemagglutinin disease (CHAD) is a relatively uncommon disorder accounting for only 15% of AIHA; it occurs mainly in the **elderly** and typically runs a **chronic course.**

CHAD is mostly benign, but the clinical features can be **very disabling and distressing**.

The patient has a chronic haemolytic anaemia aggravated by the cold and often associated with intravascular haemolysis.

Mild jaundice and splenomegaly may be present. The patient may develop acrocyanosis (purplish skin discoloration) at the tip of the nose, ears, fingers and toes caused by the agglutination of red cells in small vessels..

Haemolysis results in anaemia and the patient may be mildly icteric.

Occasionally, haemolysis dominates the clinical picture, depending on the ability of the antibody to activate complement on the red cell surface.

The cold agglutinins are monoclonal IgM κ , but serum electrophoresis may not reveal a monoclonal

band because the concentration of the protein is too low

Traditionally defined by the absence of an underlying disorder, recent studies using sensitive tests including flow-cytometry and immunohistochemical assessments have demonstrated a monoclonal CD20-positive κ-positive B-lymphocyte population

in the bone marrow of 90% of patients with CHAD. In addition, lymphoplasmacytic lymphomas are frequently associated with CHAD; therefore some authorities consider CHAD a premalignant B-cell disorder that becomes clinically overt due to the specificity of the antibody for red cell surface antigens.

In the laboratory, spontaneous agglutination of red cells is frequently observed, both macroscopically and on the peripheral blood film if made at room temperature .

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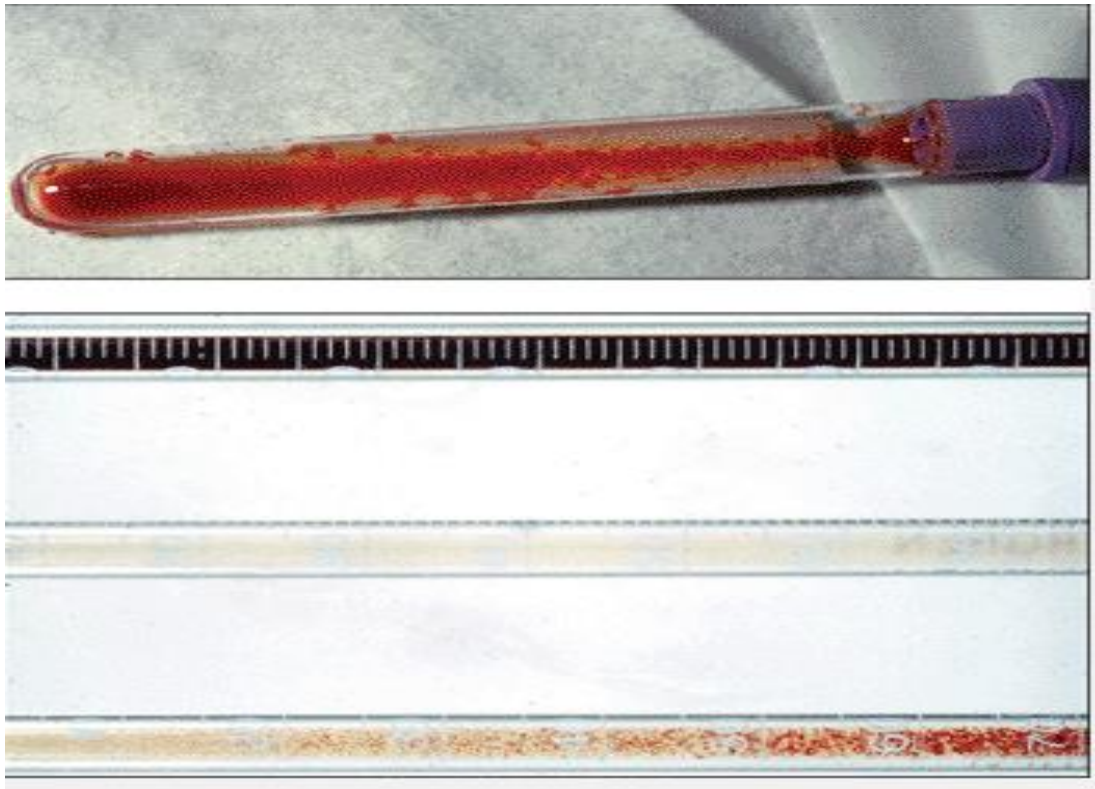
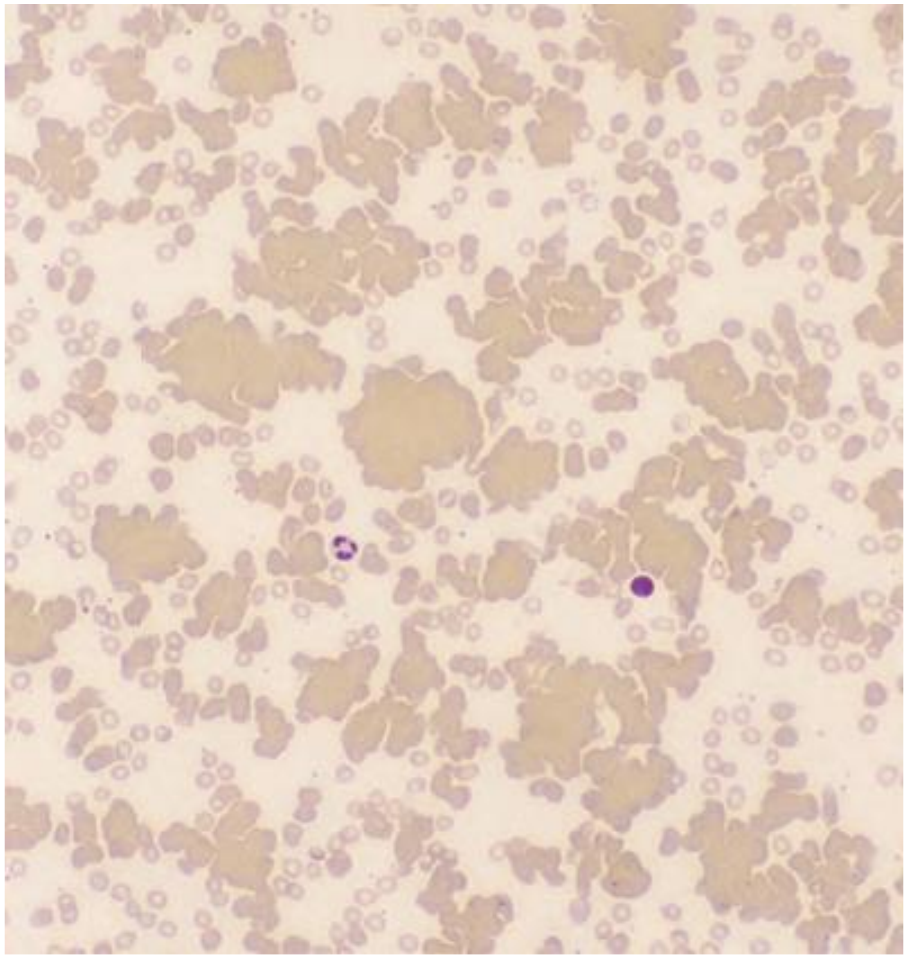
Automated blood cell counters detect agglutinates and record erroneously high mean corpuscular volume and low Hb values, unless the sample is tested at 37 °C



Blood film in cold autoimmune haemolytic anaemia. Marked red cell agglutination is present in films made at room temperature. The background is caused by the raised plasma protein concentration



DAT is positive with only C3d on the red cell surface; IgM cold agglutinins are not detected because they elute from the cell surface *in vitro*. They are usually anti-I, although anti-Pr , anti-P and other rarer specificities have been described

Infections

Infections, almost always *M. pneumoniae*, or infectious mononucleosis, may be followed by haemolysis due to cold agglutinins. Rare cases following *Listeria* or *Toxoplasma* infections have also been reported.

The antibodies are mostly polyclonal IgM in type Acute and potentially fatal episodes of intravascular haemolysis have been reported in association with *M. pneumoniae* infection.

Paroxysmal cold haemoglobinuria

-is a rare syndrome of acute intravascular haemolysis after exposure to the cold.

-It is caused by the Donath–Landsteiner antibody, an IgG antibody with specificity for the P blood group antigens, which binds to red cells in the cold but causes lysis with complement in warm conditions.

-Viral infections are predisposing causes and the condition is usually self-limiting.

Alloimmune haemolytic anaemia

Drug-induced immune haemolytic anaemia

Antibody-induced haemolytic anaemia caused by drugs is rare but, when it occurs, it can result in acute, brisk and potentially life-threatening haemolysis.

Drugs typically have a molecular weight that is too low to be immunogenic (hapten), unless they are conjugated with a larger carrier molecule such as a protein, which then allows them to elicit an immune response.

The diagnosis of drug-induced immune haemolytic anaemia should be

made in three stages:

(i) diagnosis of a DAT-positive haemolytic anaemia.

(ii) careful drug history

(iii) serological demonstration of drug-specific antibody, which interacts with red cells.

Pathogenesis

Four main mechanisms have been proposed for how drugs induce antibody-dependent haemolytic anaemia; however, the same drug at different doses or repeated usage may activate different mechanisms and there are recent suggestions that membrane modification may underlie most of the mechanisms.

1-Antibody/macrophage mediated

2-Antibody/complement mediated

3-Membrane modification

4- Autoimmune

	Drug adsorption mechanism	Immune complex mechanism	Autoimmune mechanism	Membrane modification mechanism
Examples	Penicillin Cephalosporins	Third-generation cephalosporins Quinidine Diclofenac	Methyldopa Procainamide Mefenamic acid Fludarabine* Cladribine*	Cephalosporins Cisplatin Carboplatin
Dose/duration	Large therapeutic doses/prolonged	Very low dose on second or subsequent exposure/short	Therapeutic about 6 weeks	Therapeutic
Haemolysis	Extravascular Subacute	Intravascular Acute	Extravascular Mild/subacute	Rare
DAT	IgG ± C′3	C′3 only	IgG only	IgG
Serum reaction	To drug-treated cells	Only in presence of drug or metabolite	To normal cells	To drug-treated cells
Eluate reaction	To drug-treated cells	Non-reactive	To normal cells	To drug-treated cells