

## Prevalence of autoimmune hemolytic anemia in ulcerative colitis

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### Summary

**Background:** Ulcerative colitis is a chronic idiopathic inflammatory disorder that affects the rectum & extends proximally to affect variable extent of the colon. Autoimmune hemolytic anemia had reported in few cases.

**Objective:** to determine the prevalence of autoimmune hemolytic anemia in Ulcerative colitis.

**Patient & Methods:** Fifty Iraqi patients having Ulcerative colitis attending the GIT Center in Baghdad during the period from March to August 2004 were interviewed, examined and diagnosed according to pathological study done for colonic biopsies by the same centre. Blood was drawn for the assessment of complete picture with blood film, reticulocyte percent, erythrocyte sedimentation rate, Coombs test (direct, indirect), antinuclear antibody, immunoglobulin assay, serum iron and TIBC in the same laboratory unit.

**Results:** In our study, 18(36%) patients were anemic, fifteen of them had normal or low reticulocyte percent with normochromic normocytic RBC in blood film, probable causes of anemia was either iron deficiency proved by low serum iron and high total iron binding capacity (TIBC), or anemia of chronic illness. The remaining three of eighteen patients with reticulocytosis, two of them Coombs test were negative and normal film, but they were having acute bloody diarrhea which probably was the cause of reticulocytosis.

The third patient was Coombs positive with features of hemolytic anemia in the blood film (polychromic with spherocytosis), this patient had also a high titer of IgG, LDH, so that this female had all the evidence of autoimmune hemolytic anemia which is a rare complication of Ulcerative colitis.

Sulfasalazine as a treatment of Ulcerative colitis can cause autoimmune haemolysis, but in this case the drug had stopped for one month before the development of autoimmune haemolysis.

In our sample we had five patients with reticulocytosis but normal haemoglobin level and normal blood film with coombs negative (direct and indirect) those five patients might had nonimmune causes of hemolytic like G6PD deficiency which need further investigations, or might had bloody diarrhea which cause elevated reticulocyte as a reaction to blood loss, or it may be due to salazopyrine effect which may lead to increase level of reticulocyte.

**Conclusion:** Most studies giving range of autoimmune haemolytic anaemia with Ulcerative colitis between 1%-2%, all these studies showed direct coomb's test positive, and our study showed 2% incidence. So it is one of the rare manifestations of Ulcerative colitis. It does not depend much on severity, duration and degree of colonic involvement.

**Key word:** Ulcerative colitis, autoimmune hemolytic anemia.

*J Fac Med Baghdad*  
**Vol. 50, No. 3, 2008**  
Received: April 2008  
Accepted: Aug. 2006

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### Introduction :

Ulcerative colitis is chronic idiopathic inflammatory disorder that affects the rectum and extend proximally to affect variable extend of the colon<sup>1,2</sup>.

Ulcerative colitis is worldwide disorder, although its precise incidence varies. Diagnosis may be difficult in areas where infective colitis is common, but with better diagnostic facilities and increasing medical awareness, the disease is now recognized in most countries<sup>3</sup>.

The peak age of onset is between 15- 30 years, the second peak occur between the age of 60- 80 years, male to female ratio is 1:1. The etiology of ulcerative colitis remains unknown.

40% - 50% of patients have disease limited to the rectum and rectosigmoid, 30% - 40% have disease extended beyond the sigmoid but not involving the whole colon, 20% have a total colitis<sup>2,4</sup>.

Among the miscellaneous diseases that are infrequently associated with autoimmune hemolytic anemia of the warm auto antibody type, ulcerative colitis deserves special consideration. The hemolytic anemia of the warm auto antibody type and may precede, accompany or follow the colitis<sup>5</sup>.

It is usually occurs during or after the onset of colitis, in rare cases it is precedes the colitis or begins years after proctocolectomy. Hemolytic anemia with a positive Coomb's test occurs in only 0.2% - 1.7% of patients with Ulcerative colitis<sup>6,7</sup>.

A positive Coomb's in the absence of hemolytic has also been reported in patients with ulcerative colitis, with prevalence of 1.8% in one study<sup>45</sup>.

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The findings of patients with ulcerative colitis having autoimmune hemolytic anemia were first reported in 1955<sup>8</sup>. The complication of hemolytic anemia has been shown to occur predominantly in females, but without any prediction for a particular age group<sup>7, 9</sup>. The relation between the extent or severity of the colitis and the development of hemolytic anemia is uncertain.

These findings support the theory that in some patients, the colon may be the source of autoantibody and may explain why colectomy is required to control the hemolytic anemia in some patient. Microangiopathic hemolytic anemia is also occurs in rare cases of ulcerative colitis and in sometimes associated with hemolytic uremic syndrome<sup>10,11</sup>.

### Patients and methods

Between March to August 2004 a descriptive study is carried out on fifty patients with ulcerative colitis (female, male ratio was 1: 1) attending the out patient clinic of Gastroenterology and Hepatology center in Baghdad Medical City.

They were interviewed, examined and diagnosed according to histopathological study done for colonic biopsies by the same center. Blood was drawn for the assessment of complete picture with blood film, reticulocyte percent, erythrocyte sedimentation rate, coombs test (direct, indirect), antinuclear antibody, immunoglobulin assay, serum iron and TIBC in the same laboratory unit.

### Results

There were fifty Iraqi patients with ulcerative colitis attending to Gastroenterology and Hepatology center diagnosed managed and followed up.

Table (1) and figure (1) demonstrate the age and gender of the study group, their age were between (13-61) years, 24(48%) patients were below forty years, 26 (52%) patients were more than forty years, male to female ratio was 1: 1.

Table (2) illustrate the duration of their illness were between three months and twenty nine years.

5(10%) patients had the disease less than one year, 13 (26%) patients for 1-4 years, 16(32%) patients for 5-9 years and 16 (32%) patients 10 years and more.

Table (3) and figure (2) determines the blood hemoglobin levels and packed cell volume (PCV %). The hemoglobin levels in the study were between 6-17 g\dl, 18(36%) patients were anemic. The white blood cell count (WBC), platelet count, and reticulocyte percent were demonstrated in table (4) and figure (3).

In our study the WBC count were between  $3.2 \times 10^9$  and  $16.8 \times 10^9$ , 1(2%) patients had leucopenia, 45(90%) had normal count, 4(8%) patients had leucocytosis, 1(2%) patients had eosinophilia and 1(2%) with lymphocytosis.

49(98%) patients with normal platelets count while 1(2%) patients had thrombocytosis.

Reticulocyte percent was between 0.1-6%, 42(84%) patients had normal count, 9(16%) patients had reticulocytosis ranging between (2.2% - 6%).

Table (5) and figure (4) shows the blood film of the patients 43(86%) patients had normal blood film, 1(2%) patient was showing anisocytosis, 1(2%) patient with spherocytosis, 2(4%) patients with anisopokilocytosis and 1(2%) patient with hypochromia.

Table (6) shows the results of coomb's test, the direct test positive in 1(2%) patients while indirect test was negative in all patients.

Table (7) shows the antinuclear antibody (ANA) results which were negative in 39(78%) patients and equivocal (low titre) in 11(22%) patients.

Serum immunoglobulin demonstrated in table (8) and figure (5). Serum level of IgG was between 671-2164 mg\dl. 13 (26%) patients had high titre, IgM serum level was between 30 - 1120 mg\ dl in study sample. 6(12%) patients had elevated serum IgM while IgA level was between 105.7-599.5 mg\dl, 1(2%) patient had high serum level. Table (9) and (10) showing the complete Blood picture and blood film with immunoglobulin level for those 8 patients with reticulocytosis, three of them with anemia, one of those three patients had spherocytosis with positive direct coomb's test and elevated serum IgG level, other two patients the blood film show anisocytosis, anisopokilocytosis respectively. The remaining five of the eight patients with reticulocytosis had normal haemoglobin level and blood film.

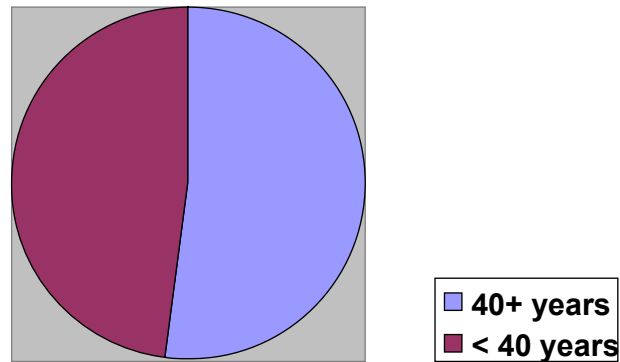
**Table 1: Frequency distribution of the study sample by age and gender.**

Age in years	N	%
<40	24	48
40+	26	52
Gender		
Female	26	52
Male	24	48

Male to female ratio is 1:1

**Table 2: Frequency distribution of the study sample by duration of the disease.**

Duration of Ulcerative colitis	N	%
< 1	5	10
1-4	13	26
5-9	16	32
10+	16	32
<b>Total</b>	<b>50</b>	<b>100</b>

**Figure1: Pie chart showing the relative frequency of different age groups in a sample of 50 patients with ulcerative colitis.****Table 3: The relative frequency of anemia defined by low Hb and PCV in a study sample of 50 patients with ulcerative colitis.**

Below normal indices (n=50)	N	%
Anemia defined by low Hb for the specific gender	18	36

**Table 4: Frequency distribution of the study sample by selected blood counts.**

	N	%
1. Total WBC count (x 1000/mi)		
Leucopenia	1	2
Within normal (4-11)	45	90
Leucocytosis	4	8
2. Platelets count		
Within normal	49	98
Thrombocytosis	1	2
3. Reticulocyte (%)		
Within normal	42	84
Reticulocytosis (> %)	8	16

Figure 2: bar chart showing the relative frequency of patients with anemia in a sample of 50 patients with ulcerative colitis

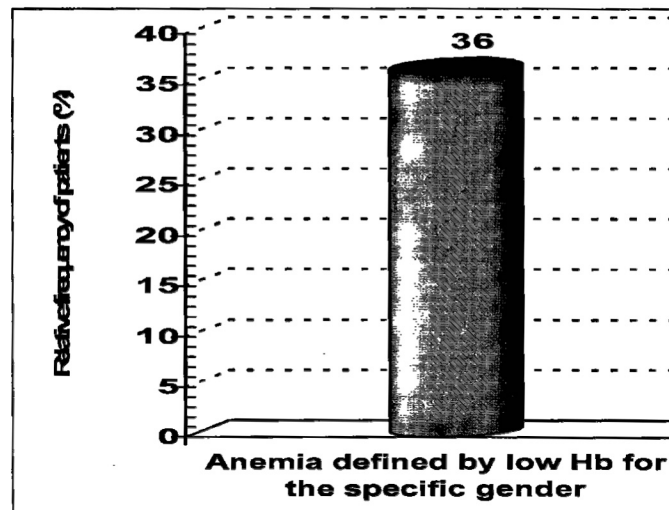


Figure 3: Bar chart showing the relative frequency of patients with selected abnormal blood count

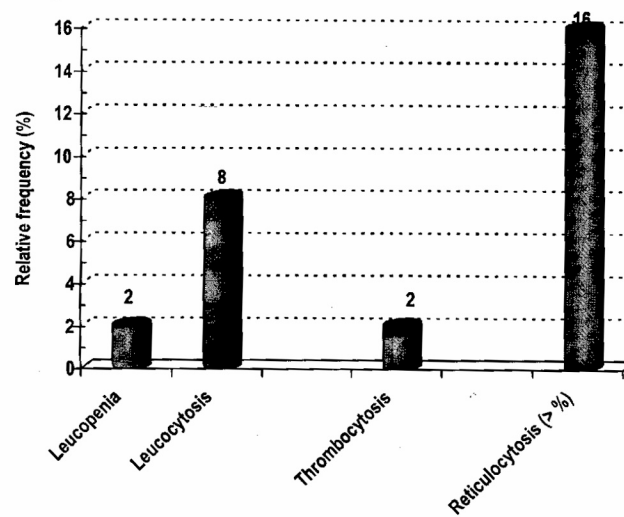


Table 5: Frequency distribution of the study sample by blood film abnormality.

Blood film	N	%
No abnormality	43	86
Anisocytosis	1	2
Eosinophilia	1	2
Lymphocytosis	1	2
Spherocytosis	1	2
Anisopiokilocytosis	2	4
Hypochromia	1	2
Total	50	100

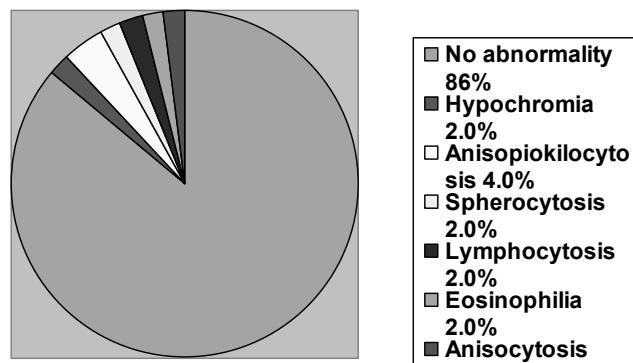


Figure 4: Pie chart showing the relative frequency of selected blood film abnormalities in a sample of 50 patients with ulcerative colitis.

Table 6: The relative frequency of positive Coomb's test in a study sample of 50 patients with ulcerative colitis.

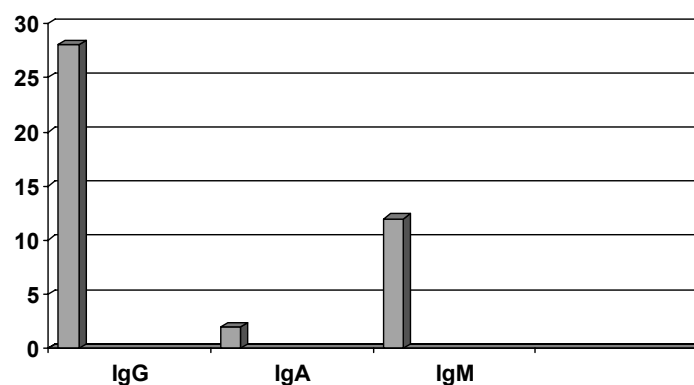
Positive Coomb's test (n=50)	N	%
Direct coomb's test	1	2
Indirect coomb's test	0	0

**Table 7: Distribution of the study sample by presence of antinuclear antibodies.**

	N	%
ANA (Antinuclear antibodies)		
Negative	39	78
Equivocal (<1:100)	11	22
<b>Total</b>	<b>50</b>	<b>100</b>

**Table 8: The relative frequency of patients with elevated levels of serum immunoglobulins concentration.**

	N	%
High serum level of immunoglobulin (n=50)		
IgG	13	26
IgA	1	2
Igm	6	12

**Figure 5: bar chart showing the relative frequency of patients with elevated levels of serum immuno-globulins concentration.**

For 8 cases with reticulocytosis:

**Table 9: Relative frequency of selected findings in subjects with reticulocytosis.**

	N	%
<i>Immunoglobulines:</i>		
High serum IgG	1	12.5
High serum IgA	0	0
High serum IgM	1	12.5
<i>Low Hh</i>	3	37.5
Positive coombs test	1	12.5
Negative coombs test	2	25

Note: None of the above cases had positive Indirect Coomb's test and none had thrombocytopenia or thrombocytosis.

**Table 10: Frequency distribution of eight cases with reticulocytosis by blood film abnormalities.**

	N	%
Blood film		
No abnormality	5	62.5
Anisocytosis	1	12.5
Spherocytosis	1	12.5
Anisopiokilocytosis	1	12.5

## Discussion

Anemia is a common complication of ulcerative colitis, its prevalence in range of 8.8%- 73.7 %<sup>(74)</sup>. It is mainly due to blood loss from gastrointestinal tract or due to anaemia of chronic illness<sup>(10)</sup>. In our study 18(36%) patients were anemic, fifteen of them had normal or low reticulocytes percent with normochromic normocytic RBC in blood film, most probable causes of their anaemia was either iron deficiency which was proved by low serum iron and high total iron binding capacity (TIBC), or anaemia of chronic illness.

The remaining three of eighteen patients had reticulocytosis, in two of them coombs test were negative and normal blood film, but they were having acute bloody diarrhea which most probably was the cause of reticulocytosis as a reaction to blood loss.

The third patient was a female aged 32 year, she had ulcerative colitis for 7 years, attended the out patient of Gastroenterology and Hepatology center for follow up, she was on sulfasalazine for last 7 years, steroid were added for her treatment before few months to control her severe disease, her hemoglobin was 9 g/dl, reticulocyte was 4%, blood film with spherocytosis, direct coombs test was negative, her total bilirubin was 2mg/dl mainly indirect. She stopped her treatment for three weeks, the patient was coming with bloody diarrhea and jaundice with splenomegally. She sent for new investigations, her hemoglobin was 7.5 g/dl, reticulocyte 6%, blood film with spherocytosis, the direct coombs test was becoming positive with high IgG level and lactate dehydrogenase (LDH), so this female had all the evidences of autoimmune hemolytic anaemia which is a rare complication of ulcerative colitis<sup>(7)</sup>.

As its known the sulfasalazine as a treatment of ulcerative colitis can cause autoimmune haemolysis<sup>(2,13)</sup>, but in this case the drug had stopped for one month before the development of autoimmune haemolysis.

Immune haemolysis is usually induced by IgG, IgM and rarely by IgA, IgE. The coombs antiglobulin test is the major tool for diagnosing autoimmune haemolysis, it is positive in 99% of cases. The direct coombs test measures the ability of anti-IgG, anti-IgM and anti-C3 antisera to agglutinate the patients RBC. The test can be negative in the presence of brisk haemolysis. The standard coombs reagent will miss IgA or IgE antibodies<sup>(2)</sup>.

Antibodies to particular RBC antigens in the serum of the patients can be detected by reacting the serum of the patient with normal RBC bearing the antigen, the latter will catch the RBC then we react the RBC with antiglobulin and this is what is called indirect coombs test<sup>(2)</sup>.

Antibody coated RBC lose membrane to macrophages in the spleen and hence spherocytes are present in the blood<sup>(14)</sup>.

Thermal specificity is used to classify immune haemolysis in the worm antibody type (bind at 37°C) and cold antibody type (bind at 4°C)<sup>(13)</sup>.

The warm type account for 80% of cases, the majority are IgG antibodies, its incidence in general population was 1/100000<sup>(13)</sup>.

Autoimmune haemolysis complicate ulcerative colitis is of warm antibody type, the origin of these antibodies had been hypothesized that absorption of non-red-cell antigens across the diseased colonic mucosa leads to the production of antibodies that cross react with erythrocytes and in some cases result in autoimmune haemolysis<sup>(15)</sup>.

In our study the prevalence of coombs positive haemolytic anaemia was only 1(2%) patients. This finding is consistent with that described by a study made by Dr. Raghad J. Al-Akashi in the Gastroenterology and Hepatology center between 1998-1999, they were diagnose 130 cases of chronic colitis of which 77 case with ulcerative colitis, there was only one case with autoimmune haemolytic anaemia as associated condition with Ulcerative colitis<sup>(16)</sup>.

Another study made in Mount Sinai School of Medicine of the City University of New York, they had taken 1150 patients with Ulcerative colitis, the prevalence of coombs positive haemolytic anaemia in the study sample was 8(0.7%) patients with female preponderance (F:M= 7: 1).

The haemolytic anaemia appeared at a mean of 10 years after the onset of colitis, apparently independent of the age of the patient; our case had developed haemolysis in her seventh year of illness. Although seven of the eight patients had active colitis at the time of diagnosis of anaemia as our case had, there was no consistent relationship to the extent of the bowel disease. Seven of the eight patients survived. One patient showed partial response to steroid therapy, as did our case, two responded to splenectomy, but four required both colectomy and splenectomy. Steroid should be the first line of therapy followed by splenectomy, if necessary. For those patients who have severe colitis which in itself would merit surgery, total proctocolectomy combined with splenectomy seems advisable<sup>(15)</sup>.

While another study performed in the department of Gastroenterology and Haematology University Hospital of Heraklion, Crete, Greece, they had 302 patients with U.C., the prevalence of coombs positive haemolytic anaemia in that sample was 5(1.7%) patients with male preponderance (M: F= 2: 1), one more patient developed coombs positive haemolytic anaemia attributed to sulfasalazine. Autoimmune haemolytic anaemia occurred during active colitis in all cases. The mean time between the onset of colitis and the diagnosis



of autoimmune hemolytic anemia was 17 months, three of five (60%) patients with autoimmune hemolytic anaemia had total colitis. All 5 patients were treated initially with large doses of corticosteroids. Three of five (60%) had good hematological responses one patient responded to the addition of azathioprine and one underwent splenectomy and proctocolectomy<sup>(7)</sup>.

This difference in the results between our study and the last two above studies probably due to the size of the sample taken. In our sample we had five patients with reticulocytosis but normal hemoglobin level and normal blood film with coombs negative (direct and indirect) those five patient might had non immune causes of haemolysis like G6PD deficiency which need further investigations, or might had bloody diarrhoea which cause elevated reticulocyte as a reaction to blood loss, or it may be due to salazopyrine effect which may lead to increase level of reticulocyte.

### Conclusion

Most studies giving range of autoimmune haemolytic anaemia with Ulcerative colitis between 1%-2%, all these studies showed direct coomb's test positive, and our study showed 2% incidence.

So it is one of the rare manifestations of Ulcerative colitis. It does not depend much on severity, duration and degree of colonic involvement.

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