

# Pernicious Anemia in Arabs

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**ABSTRACT:** Over a nine-year period extending from January 1986 to December 1994, eighteen cases of pernicious anemia occurring in Arabs were diagnosed at King Khalid University Hospital in Riyadh. There were 12 Saudi Arab patients and 6 non-Saudi Arabs. There were 11 males and 7 females. The mean age at presentation was 51 years. The presenting symptoms, laboratory features and the disease pattern were similar to those described in northern European patients in most respects with two possible exceptions. First, the mean age at presentation was lower and second, there was a higher frequency of the antibody to intrinsic factor than previously described in northern Europeans. Both differences have been previously noted in Blacks. Associated autoimmune diseases were identified in two patients, one of whom had diabetes mellitus and vitiligo while the other had a remote history of Graves' disease. One young female patient with primary infertility successfully conceived shortly following the initiation of appropriate cyanocobalamin therapy.

**Keywords:** anemia, pernicious, megaloblastic, macrocytic, B<sub>12</sub> deficiency, Arabs, Saudi Arabia

## INTRODUCTION

Pernicious anemia (PA) predominates in people of northern European origin but may affect others more often than previously thought. Arabs are among the ethnic groups described to be rarely affected by PA (1). Only few case reports and very small series have been published in the English medical literature (2,3). In this report, we describe details of the clinical, laboratory and immunologic features in eighteen Arab patients with PA seen at our institution. Seven Saudi Arab patients out of these eighteen have been previously reported from our institution (4). To the best of our knowledge, this is the first report to describe a series of Arab patients with PA.

## PATIENTS AND METHODS

Between January 1986 and December 1994 a total of 25 cases with megaloblastic anemia occurring in adult Arab patients were diagnosed at King Khalid University Hospital in Riyadh. Four of these patients had no etiological diagnosis because of incomplete work-up. Another three patients were found to have folate deficiency. The remaining 18 patients had PA.

The criteria used for diagnosis of PA were similar to those proposed by Lindenbaum in 1983 (5); namely i) the presence of megaloblastic bone marrow, ii) subnormal serum vitamin B<sub>12</sub> level, iii) characteristic vitamin B<sub>12</sub> absorption (Schilling) test or the presence in the serum of antibodies to the intrinsic factor (AIFA).

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None of the patients had had previous gastrectomy or ileal resection. In addition to detailed history and physical examination at presentation, all 18 patients underwent full hematological evaluation including bone marrow examination, biochemical testing for blood glucose levels, renal function, bilirubin and hepatic enzymes, and thyroid indices. Serum vitamin B<sub>12</sub> and folate levels were measured by radioimmunoassay (vitamin B<sub>12</sub>/folate dual RIA kit, Amersham, UK). Fasting gastric fluid pH determination and gastric biopsy were obtained in 16 patients.

All patients were tested for the presence of the AIFA using the ELISA technique (Cambridge Life Science, Cambridgeshire, UK). Fifteen patients were tested for the presence of the anti-parietal cell antibodies (APCA) using an indirect immunofluorescence technique (Fluoro-Kit Test Systems, INCSTAR Corporation, Minnesota, USA). Dual isotope Schilling test (Dicopac kit, Amersham, UK) was carried out in five patients. Two capsules, one containing <sup>57</sup>Co cyanocobalamin bound to intrinsic factor and the other

containing free <sup>58</sup>Co cyanocobalamin were given orally to each of the five patients. This was immediately followed by 1000 µg of non-radioactive vitamin B<sub>12</sub> given intramuscularly as a flushing dose. Differential counting of the isotope was then carried out on a 24-hour urine specimen. A <sup>57</sup>Co/<sup>58</sup>Co urinary B<sub>12</sub> ratio of >1.8 was considered a positive test for intrinsic factor deficiency.

All patients received intramuscular vitamin B<sub>12</sub> therapy. Fourteen patients were initially treated with 1000 µg cyanocobalamin daily for three consecutive days followed by monthly injections of the same dose of vitamin B<sub>12</sub> while the remaining four patients received 1000 µg of cyanocobalamin daily for three consecutive days, followed by weekly injection of the same dose for four weeks and were maintained on monthly injection thereafter. All patients were also given 5 mg of folic acid daily in conjunction with parenteral B<sub>12</sub> from the time of diagnosis of megaloblastic anemia was made until the diagnosis of vitamin B<sub>12</sub> deficiency was established.

Table 1. Symptoms at presentation in 18 Arabs with PA

Symptom	Number of Patients	Percent
Fatigue	13	72%
Symptoms of anemia	11	61%
Anorexia	3	17%
Weight loss	2	11%
Neurological symptoms	2	11%
Fever	1	6%
Dyspepsia	1	6%
Symptoms of diabetes	1	6%
Vitiligo	1	6%
Primary infertility	1	6%
Painful tongue	1	6%
Symptoms of thyroidism	0	0%
Premature greying of hair	0	0%

Table 2. Physical findings at presentation in 18 Arabs with PA

Sign	Number of Patients	Percent
Pallor	16	89%
Glossitis or smooth tongue	3	17%
Jaundice	4	22%
Peripheral neuropathy	2	11%
Skin pigmentary changes	1	6%
Heart failure	1	6%
Posterior column signs	0	0%
Goiter	0	0%
Signs of thyroid disease	0	0%

Table 3. Laboratory parameters at presentation in 18 Arab patients with PA

Parameter	Mean $\pm$ SD	Range
White blood cells ( $\times 10^9 / l$ )	5.34 $\pm$ 1.42	2.1 - 8.0
Hemoglobin ( Grams / l )	72.83 $\pm$ 23.26	44 - 135
Hematocrit (%)	22.39 $\pm$ 7.70	13.2 - 40.0
Mean corpuscular volume (fl)	112.13 $\pm$ 13.76	84.0 - 127
Platelets count ( $\times 10^9 / l$ )	202.61 $\pm$ 94.78	60.0 - 322.0
Lactate dehydrogenase (iu/l)	1535.14 $\pm$ 1170.69	427 - 4304
Serum bilirubin ( $\mu\text{mol} / l$ )	31.50 $\pm$ 15.00	13 - 55
Vitamin B 12 level*	31.56 $\pm$ 13.95	12 - 56

\* Normal range 165 - 920 pg/ml

Table 4. Results of diagnostic workup

Test	Patients Studied (n)	Results
Bone Marrow	18	Megaloblastic in 18 (100%)
Fasting Gastric pH	16	6.8 $\pm$ 0.87 (mean $\pm$ SD) Range 4.0-8.0
Gastric Pathology	16	Atrophic gastritis in 10 Normal in 6 (37.5%)
Schilling Test	5	Positive in 5 (100%)
AIFA	18	Detectable in 16 (89%)
APCA	15	Detectable in 12 (80%)

## RESULTS

### *Patient Characteristics*

There were 11 males and 7 females with a mean age of  $51 \pm 15.7$  (mean  $\pm$  SD) years ranging from 23 to 73 years. There were 12 Saudis and 6 non-Saudi Arab patients (3 from Egypt, 2 from Israel and one from the Sudan).

### *Clinical Features at Presentation*

The most frequent symptom at presentation was fatigue which was reported by more than half of the patients. The most frequent sign at presentation was, as expected, pallor. Other presenting symptoms and signs are outlined in tables (1) and (2) respectively.

### *Diagnostic Studies*

All patients had normal renal and hepatic function tests. Seventeen patients had normal blood glucose levels while one patient, who was known to have diabetes mellitus, had fasting hyperglycemia. One patient who has had subtotal thyroidectomy for Grave's disease in the past was found to have slightly elevated TSH level despite her thyroxin replacement therapy. Serum and red cell folate levels were normal or high in all patients. Two patients were found to have concurrent  $\beta$ -thalassemia minor. The results of the hematological values and the diagnostic tests are shown in tables (3) and (4) respectively.

### *Response To Therapy*

Reticulocytosis was first detected after  $4 \pm 1.8$  days (mean  $\pm$  SD). All patients except the two with beta-thalassemia trait, normalized their hemoglobin levels within 5-10 weeks of treatment. Both patients with thalassemia minor maintained a subnormal hemoglobin level associated with microcytosis for several months after commencing therapy. The leukocyte and platelets counts returned to normal values in all patients within two weeks of treatment.

## DISCUSSION

Although PA has been traditionally considered to be a disease of people of northern European origin, recent surveys in racial groups in whom the disease was widely regarded as rare such as American Blacks, American Indians, Latin Americans and Asians suggest a higher incidence in them than previously thought (6-10). Arabs are considered to be among the racial groups that are rarely affected by PA (1). The first report of possible PA in two Arab patients came out of Iraq in 1952 (11). Three additional cases were reported from Kuwait in 1970 (12). Few case reports have appeared in the English medical literature since (2,3,13,14). A series of seven Saudi Arab patients with PA, all of whom are included in this report, was reported by our group (4) and has been, to the best of our knowledge, the largest series to date to be published on this topic.

The disease in our group of Arab patients had many similarities to that described in medical textbooks predominantly occurring in northern Europeans. There were, however, two main differences. The first, a mean age at presentation of 51 years is in contrast to the 60-70 years reported in Europeans and Americans (6). A younger age at presentation has been previously observed in American and South African Blacks (7). A second notable difference was the higher frequency of AIFA than that reported in northern Europeans (89% versus 55-70%) (1,15,16). Again a similar high AIFA detection rate has been observed in black American women (6,7). The frequency of the APCA detection was 80% and was not different from the reported rate (1).

A notable observation in this series, despite its small size, is the male predominance. This contrasts with the higher female or at least approximately equal sex incidence reported in Caucasians (1,17). Despite a male to female ratio in our series of 1.6:1, the difference did not reach the level of statistical significance because of the small number of patients. It is of interest to note that most of the patients described in previous reports were males. Thus the higher incidence of the disease in Arab males might be an additional

difference from the disease in Europeans.

It is generally accepted that the frequency of leukopenia and thrombocytopenia is related to the severity of anemia, being higher when the hematocrit falls below 25% (1). This was not well-demonstrated in our series. Only two patients had leukopenia and four patients had thrombocytopenia with only two of those showing significant thrombocytopenia despite the fact that 12 patients had hematocrit values below 25%.

Two patients demonstrated the interesting phenomenon of masking the macrocytosis of PA by the concurrent occurrence of  $\beta$ -thalassemia trait. This phenomenon has been reported to occur with both  $\alpha$ - and  $\beta$ -thalassemia carrier states as well as with iron deficiency anemia (18-21). The mean corpuscular volume in these two patients was within the normal range at the time of diagnosis of PA but dropped to the microcytic range with cyanocobalamin therapy.

Another young female patient presented with two-year history of primary infertility. Successful conception occurred six weeks following the initiation of vitamin B<sub>12</sub> treatment. As PA is rarely encountered in women in the child-bearing age, infertility is quite often omitted when rare manifestations of PA are discussed. The association between PA and infertility in both males and females has been described in several reports (22-24).

This series of Arab patients with PA points out that although the disease is considered rare among Arabs, it should be considered in the workup of any patient with macrocytic anemia. In addition, due to the high carrier rate of the thalassaemic gene in the region, physicians should consider the diagnosis of PA even in the absence of frank macrocytosis if the clinical setting suggests an acquired, unexplained, normocytic anemia in middle aged and elderly Arab patients. The later statement is also applicable to young infertile women with significant degree of anemia.

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