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Clinicopathological Characteristics of Pernicious Anemia: A Study of 300 Patients in Turkey

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RB and IB were responsible for reviewing previous research, journal hand searching and drafting of the report. Authors MAE, EG, IN, EK, IK and MK contributed to the final draft of the manuscript and the analysis of relevant data. Author IA was responsible for project coordination. All the authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Our study was undertaken to examine the laboratory and clinical features of pernicious anemia patients presenting initially at the Turgut Ozal Medical Center, which serves as an important tertiary health center in Eastern Anatolia.
Study Design: Among patients evaluated for etiology of anemia, we analysed the clinicopathological characteristics of 300 (158 females and 142 males) patients with pernicious anemia retrospectively.
Place and Duration of Study: Department of Internal Medicine and Division of Hematology, Inonu University School of Medicine, between 1996 and July 2011.
Methodology: Full blood counts, thyroid hormone levels, liver function tests and LDH levels

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were reviewed for 300 patients with pernicious anemia retrospectively. Peripheral blood smears and bone marrow biopsies were reviewed by a hematologist. Endoscopic examination and ultrasonographic inspection were performed for atrophic gastritis, gallbladder stones and hepatosplenomegaly for all patients. Laboratory values, ages, signs and symptoms of patients at the time of diagnosis were compared between genders.

Results: The mean age of the female patients was 50.56 ± 17.75 years (17–84), while that of the male patients was 57.24 ± 15.78 (20–95) years. At the time of diagnosis, the male patients were older than the females (p = 0.002). LDH levels were significantly higher for females (p = 0.043). The incidence of gallstones was significantly higher in females (25.4%) than in males (10.7%) (p = 0,001). Pancytopenia was defined as a hemoglobin level lower than 10 gr/dl, leukocytes lower than 1.500/µL and platelets lower than 150.000/µL and the incidence of pancytopenia was 41.3% (n = 65) and 50.7% (n = 71) in the female and male patients, respectively, and the difference was not statistically significant. There was no statistically significant difference for frequency of thyroid disease or symptoms and signs at the time of diagnosis between genders.

Conclusions: Pernicious anemia is not a disease of only elderly women; it can be seen in both men and women of younger ages. It is seen nearly as often in women as in men. Gallstones and abnormal thyroid activity can be observed at these patients at the time of diagnosis; therefore, these findings should be considered.

Keywords: Pernicious; anemia; clinicopathologic; gender.

1. INTRODUCTION

Pernicious anemia (PA) is the most common cause of vitamin B12 deficiency. It is a chronic disease caused by the deficiency of intrinsic factor [1]. The annual incidence of pernicious anemia is approximately 25 new cases per 100,000 persons older than 40 years. Although the average age of onset is approximately 60 years, it is increasingly encountered in people 5 to 10 years younger [2]. PA is more common in people in Northern Europe, England, and Ireland. It is usually seen after the age of 50, although PA may start earlier in American and African Blacks. PA starts earlier and has a higher prevalence among women in Turkey than those in Western society [3]. PA occurs in nearly 1% of those over 60 years of northern European origin [4,5]. Indians of East African origin have exactly the same incidence of PA as the indigenous population of the United Kingdom [1,6]. While some studies have confirmed the female preponderance described [3,7,8], others have not confirmed the female preponderance [9-11]. Commonly overlooked symptoms include: fatigue, depression, low-grade fevers, nausea, gastrointestinal symptoms (heartburn, diarrhoea, dyspepsia), weight loss, jaundice, glossitis (swollen, red and smooth appearance of the tongue), angular chelitis and neurological symptoms (unsteady gait, spasticity, stiffness and tightness in the muscles), and peripheral neuropathy (damage to the nerves in your arms and legs, progressive lesions of the spinal cord , memory loss) [4], Approximately 50% of patients develop clinical or latent thyroid disease, most often hypothyroidism [12]. In Turkey, the prevalence of gallbladder stones is 32.2% in PA patients [13]. In this study, we evaluated the clinicopathologic characteristics of PA among patients from a tertiary health center in Eastern Anatolia between 1996 and 2011.

2. MATERIALS AND METHODS

Between 1996 and 2011, 316 patients diagnosed with PA in the Hematology Department of the Inonu University Turgut Ozal Medical Center among patients evaluated for etiology of anemia were considered for this retrospective study. Sixteen patients were excluded from the evaluation due to lack of data. All patients were admitted for the differential diagnosis of anemia. Drugs and diseases that cause high mean corpuscular volume (MCV) were carefully considered. All patients were evaluated with a full medical history and physical examination. Particular attention was paid to their dietary habits, alcohol intake, previous gastric operation, past or concomitant autoimmune disease and any symptoms or signs of anemia, infection, bleeding or disorders affecting the neurological and gastrointestinal systems. Validation of the diagnosis of PA was based on all of the following criteria: demonstration of atrophic gastritis by endoscopic examination, megaloblastic changes in bone marrow biopsy, the absence of other reasons for recognizable B12 deficiency, normal serum folate levels low serum vitamin B12 levels (cyanocobalamin) elevation of lactate dehydrogenase (LDH) and indirect bilirubin, satisfactory response to parenteral B12 and one or combination of hypersegmentation and macrocytosis in the peripheral blood, ; serum intrinsic factor antibody. Serum antibody to intrinsic factor and Schilling tests could not performed on all patients due to a lack of technical facilities. Anti-parietal cell antibodies also could not be evaluated for any patient for the same reason. Full blood counts were performed, and the Mean Corpusculer Volume (MCV) was measured using a Coulter Haematology Analyser (STKS Coulter Electronics Inc., Miami, USA). Peripheral blood smears were reviewed by a hematologist. Hypersegmentation of neutrophils was defined as the presence of 5% or more five-lobed neutrophils or one or more six-lobed neutrophils.[9] Bone marrow examination was performed with the patients' consent, and megaloblastic hematopoiesis was evaluated. Immulite 2000 (Siemens/DPC, USA) with the chemiluminescence immunoassay method was employed for serum cobalamin assay. Patients were referred for the test after their cobalamin deficiency was corrected. Thyroid function tests were performed for all patients to determine the levels of thyroid-stimulating hormone and free thyroxine.

The symptoms and signs of vitamin B12 deficiency vary. To determine the presence of neuropathy, the following symptoms were asked about: loss of sensation of vibration and position, weakness, palpitation (abnormality of heartbeat), jaundice (yellowish pigmentation of the skin), chronic diarrhea (diarrhea longer than three weeks), weight loss, anorexia (decreased sensation of appetite), paleness, forgetfulness, visual problems, loss of memory, urinary incontinence (the involuntary excretion of urine) and/or fecal incontinence (the involuntary excretion of bowel contents), impotence, abnormal taste and odor sensation and decreased reflexes. A variety of laboratory findings of cobalamin deficiency were observed, including anemia, reticulocytopenia, macrocytosis, neutropenia, thrombocytopenia, hypersegmentation of the neutrophils, elevated lactate dehydrogenase and increased unconjugated bilirubin in the serum.

Endoscopic examination and ultrasonographic inspection were undertaken for all patients and viewed for atrophic gastritis, gallbladder stones and hepatosplenomegaly. Cobalamin was administered with a dosage of 1 mg/day intramuscularly for fifteen consecutive days, followed by weekly injections for improvement of the hemoglobulin levels and once a month thereafter for life. Data for patients who did not respond to cobalamin therapy were excluded from the study.

3. STATISTICAL ANALYSIS

Comparisons between genders were performed using the unpaired Student's t-test. Results are expressed as the mean ± standard deviation. The signs and symptoms ratio of the study groups were analysed using the chi-square test. The SPSS 16.0 software package (SPSS Inc. Chicago, IL, USA) was used for the statistical analyses. $P < 0.05$ was considered significant.

4. RESULTS

The criteria for pernicious anemia was met by 316 patients diagnosed with megaloblastic anemia. Data for 16 patients were excluded due to lack of data. Although the disease is seen more frequently in women, our gender rate was nearly even, as 47.3% (n = 142) of patients were male and 52.7% were female (n = 158). The mean age of the females was 50.56 ± 17.3 years (ranging from 17–84); men's mean age was 57.45 ± 15.9 years (ranging from 20–95). The difference between these two groups was statistically significant (p = 0.002). In the age distribution, 34 women and 55 men were older than 60 years. The mean LDH levels of patients were 5003.57 ± 384.45 for females and 3920.23 ± 338.36 for males. There was a statistically significant difference in LDH level between the groups (p = 0.043). The age and laboratory values for patients are shown in Table 1.

Table 1. Age and laboratory values for patients

Variable/Normal range	Male (n = 142)	Female (n = 158)	p
Age, years	57.45 ± 15.9	50.56 ± 17.3	**0.002**
Hgb (Male: 13–16 g/dL) (Female: 12–15 g/dL)	7.1 ± 2.7	6.8 ± 2.2	>0.05
MCV (80–95 fL)	112.2 ± 12.0	109.6 ± 14.1	>0.05
RBC (3.5–5.5x10^6 µL)	2.15 ± 1.0	1.95 ± 1.0	>0.05
WBC (4–10x10^3 µL)	4.3 ± 2.3	4.3 ± 2.1	>0.05
Plt (150–450x10^3 µL)	113.9 ± 84.1	134.0 ± 78.4	>0.05
I.Bil (0.25-0.75 mg/dL)	1.4 ± 1.1	1.3 ± 1.1	>0.05
LDH (143–254 U/L)	3920.23 ± 338.36	5003.57 ± 384.45	**0.043**
K^+ (3.5–5.5 mmol/L)	4.3 ± 0.5	4.1 ± 0.4	>0.05
free-T3 (1.8-4.2 pg/mL)	2.8 ± 1.1	2.9 ± 1.1	>0.05
free-T4 (0.8-1.9 ng/dL)	1.1 ± 0.2	1.5 ± 1.5	>0.05
TSH. (0.4-4 mIU/mL)	1.7 ± 1.4	1.9 ± 1.9	>0.05
AST (5-34 U/L)	47.4 ± 45.5	44.2 ± 32.1	>0.05
ALT (0-55 U/L)	32.2 ± 42.4	27.6 ± 25.4	>0.05

Variables shown as mean ± SD.
p values are generated by Student's t test to compare males and females

The incidence of pancytopenia in female patients was 42% (n = 66), and it was 50.6% (n = 72) in male patients. In females, the incidence of gallstones was significantly higher than in males (25.3% for females vs. 10.7% for males, p < 0.001). The frequency of neuropathy was 12% in females and 10% in males, and the difference was not statistically significant. The frequency of male patients with hyperthyroidism and hypothyroidism was 9.3% and 8.7%, respectively. These rates were 10% and 12%, respectively, for females. The differences were not statistically significant. Atrophic glossitis was not significantly different between males and females (51.3% for females, 58.6% for males, p > 0.05). There was no

statistically significant difference ($p > 0.05$) in the incidence of signs and symptoms (such as weakness, palpitation, jaundice, anorexia or paleness) between male and female patients (Table 2).

Table 2. The signs and symptoms of patients

Variable	Male (n = 142)	Female (n = 158)	All (n = 300)	p
Gallstones	10.7% (n = 16)	25.3% (38)	18% (54)	< 0.001
Hypothyroidism	14 (9.8%)	18 (11.8%)	32 (10.6%)	>0.05
Hyperthyroidism	13 (9.1%)	15 (9.4%)	28 (9.3%)	>0.05
Splenomegaly	10 (7.0%)	14 (8.8%)	24 (8%)	>0.05
Hepatomegaly	11 (7.7%)	6 (3.7%)	17 (5.7%)	>0.05
Neuropathy	15 (10.5%)	18 (11.3%)	33 (11%)	>0.05
Pancytopenia	76 (53.5%)	63 (39.8%)	139 (46.3%)	>0.05
Atrophic glossitis	77 (54.2%)	88 (55.6%)	165 (55%)	>0.05
Weakness	129 (90.8%)	143 (90.5%)	272 (90.7%)	>0.05
Palpitation	77 (54.2%)	93 (58.8%)	170 (56.7%)	>0.05
Jaundice	25 (17.6%)	25 (15.8%)	50 (16.7%)	>0.05
Chronic diarrhea	15 (10.5%)	10 (6.3%)	25 (8.3%)	>0.05
Weight loss	17 (11.9%)	15 (9.4%)	32 (10.7%)	>0.05
Anorexia	50 (35.2%)	59 (37.3%)	109 (36.3%)	>0.05
Paleness	111 (78.1%)	116 (73.4%)	227 (75.7%)	>0.05
Forgetfulness	15 (10.5%)	20 (12.6%)	35 (11.7%)	>0.05
Use of PPI	5 (3.5%)	3 (1.8%)	8 (2.7%)	>0.05
Gallstones	16 (11.2%)	38 (24.0%)	54 (18%)	< 0.001

Hypersegmented neutrophils, defined as the presence of 5% or more five-lobed neutrophils or 1% or more six-lobed neutrophils were detected in the peripheral blood of 86.7% (130) of male patients and 87.3% (131) of female patients. Macroovalocytosis was found in 94.7% (142) of male patients and 93.3% (140) female patients. There was no statistically significant difference ($p > 0.05$) in the peripheral blood smear findings between male and female patients (Table 3).

Table 3. Peripheral blood smear findings of patients

Variable	Male (n = 142)	Female (n = 158)	p
Hypersegmentation	130 (91.5%)	131 (82.9%)	>0.05
Macroovalocytosis	142 (100%)	140 (88.6%)	>0.05
Cabot's rings	27 (19%)	32 (20.2%)	>0.05
Normoblast	47 (33.0%)	35 (22.1%)	>0.05
Basofilic stippling	18 (12.6%)	22 (13.9%)	>0.05
Teardrop	8 (5.6%)	7 (4.4%)	>0.05

5. DISCUSSION

To the present authors' knowledge, the current study includes the largest number of Turkish patients with PA reported to date and shows some significant hematologic and clinical features of PA in Turkish people. Kocak and Paydas reported on a cohort of 44 PA patients

during a five-year period in Turkey [3]. A separate cohort of 59 patients has been reported during a four-year period in our centre [13].

PA was the cause of megaloblastic anemia in 66.2% of 453 patients diagnosed with megaloblastic anemia at our hospital over 15 years. In a study with findings consistent with our results performed in Israel and other Middle Eastern countries, this rate was 69% (n = 203) [14]. In another study previously conducted in Turkey among 200 patients admitted for anemia to a hospital, 44 were found to have megaloblastic anemia caused by probable PA [13].

Female patients with PA are affected almost 50% more often than men in most surveys. A female preponderance ranging from 1.7 to 2.0:1 has been reported in White subjects [7,8]. This sex distribution has been confirmed in a population survey of people older than 60 years that was conducted in California, in which the prevalence of PA was 2.7% in women and 1.4% in men [15]. However, data reported concerning American, Japanese and Italian PA patients seem not to confirm the female preponderance described in older studies [9-11]. Similarly, there was no significant female predominance in the distribution of our patients.

The mean age of PA patients in published studies ranges from 59 to 62 years [9, 10, 11, 16]. The mean age of our male patients was similar to these data. The current study showed that the mean ages of our patients with PA at presentation in males and females were 57 and 50 years, respectively. In the age distribution, 34 of all female patients and 55 of all male patients were older than 60 years. In other words, about two-thirds of male patients and four-fifths of female patients were younger than 60 years old. PA in our patients is, hence, a disease of those under the age of 74 years, and the mean age does not resemble that of Whites, who exhibit a peak incidence above 60 years of age [7]. *H. pylori* seropositivity in this age group is over 80% in our country [17]. Consequently, the incidence of atrophic gastritis can be high. Menstrual blood loss in these patients leads to profound anemia and can cause admission to a clinic earlier. This may be the cause of the disease being seen in women of younger ages.

PA is the end-stage of atrophic gastritis and is generally considered an autoimmune disease. The autoimmune origin of PA is based on the presence of parietal cell and/or intrinsic factor autoantibodies and is frequently associated with other autoimmune disorders, such as autoimmune thyroid disease, type 1 diabetes and vitiligo [18-20]. We could not demonstrate the parietal cell and/or intrinsic factor antibodies in our patients due to lack of technical facilities; instead, we used laboratory tests, clinical evaluation and pathological demonstration of atrophic gastritis as a means of diagnosing PA.

There is now strong evidence to support the presence of a true association between PA and autoimmune thyroid disease. Among Whites, Carmel and Spencer demonstrated that 24.1% of patients with PA had clinical autoimmune thyroid disease [12]. Similarly, hypothyroidism and hyperthyroidism were observed in 10.7% and 9.3% of our patient population, respectively. These rates were close to those reported among Chinese patients [21] and in the literature [22].

Pancytopenia refers to a reduction in all three elements that form blood: red blood cells (hemoglobin <10 gr/dl), white blood cells (leukocytes <1500/µL) and platelets (platelets <150.000/µL). Aplastic anemia and megaloblastic anemia were the most common causes of pancytopenia in Zimbabwe and India [23, 24]. We have seen that the rate of pancytopenia in patients with pernicious anemia has not been reported before in the literature. The incidence

of pancytopenia in our patients was 46.3% (n = 139). The pancytopenia in patients with PA can mimic aplastic anemia, which is also usually macrocytic but does not display bilirubin and lactate dehydrogenase elevations. Therefore, if LDH and bilirubin levels are high in patients with pancytopenia, PA should be considered in the diagnosis.

Ineffective erythropoiesis and intramedullary hemolysis are the two important results of PA. Hemolysis is one of the risk factors in the formation of gallbladder stones. An increased frequency of gallstones was also suggested in our study. Aydogdu et al. detected that 32.2% of patients in the pernicious anemia group had gallstones [13]. Gallstones rates were 25.3% in females, 10.7% in males and 18% in all patients in our study ($p < 0.001$). Female gender is an important risk factor for gallstones. Gallstones are more prevalent in females than males in all adult age groups, with ratios exceeding 3:1 in women in their reproductive years and falling to under 2:1 in people over 70 years of age [25]. In our study, there was a female predominance in having gallbladder stones in the distribution of our patients, which is consistent with the literature results.

Although splenomegaly is a well-known finding in patients with PA, modern textbooks do not mention this as a finding associated with the disease. Early studies include palpable splenomegaly as a common finding in pernicious anemia [26-28]. MacCarty reported his experience with 51 patients with pernicious anemia diagnosed at the Mayo Clinic, where splenomegaly was found in 45% of the cases [26]. However, in a study of 200 patients conducted by Bigg, spleen size was found to have increased in only 3% of the patients [28]. In our study group, splenomegaly was found in 8% of patients (6.7% of males, 9.3% of females).

The serum LDH concentration usually is markedly increased in pernicious anemia [4]. There are no data concerning between LDH levels and age, gender of patients with pernicious anemia in the literature. LDH levels were high in women patients with PA in our study because the mean age of women patients is younger than that of men, presumably as a result, intramedullary hemolysis is further composed and LDH may be higher in women patients.

The limitations of our study included the fact that serum antibody to intrinsic factor, anti-parietal cell antibody and Schilling tests could not performed on all patients due to a lack of technical facilities.

6. CONCLUSION

This is the largest study in terms of the number of patients analysed related to PA reported to date. PA is not a disease of elderly women but can be seen in both genders at a younger age. The incidence of gallstone in patients with PA was high, as reported in our clinic again within the last decade. Gallstones should be considered in patients with PA at diagnosis, and splenomegaly is not common and can be underestimated. In addition, thyroid disease should be kept in mind concerning patients with PA due to its high prevalence at diagnosis.

CONSENT

Written informed consent was obtained from the patients' next of kin for publication of this manuscript and accompanying images.

ETHICAL APPROVAL

The study was approved by the Ethics Committee. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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