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Haematological manifestations in primary hyperparathyroidism

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***Background & objectives*: Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused by the elevated secretion of the parathormone (PTH). The aim of this study was to evaluate the haematological manifestations of PHPT in patients with normal renal functions who were treated surgically for parathyroid adenomas.**

***Methods*: In this retrospective cross-sectional study, 134 patients with normal renal functions who underwent parathyroidectomies for PHPT were included. The haematological manifestations were evaluated in the total study cohort and in the two groups of different calcium (Ca) levels (Group 1 ≤11.2 mg/dl and Group 2 >11.2 mg/dl).**

***Results*: The overall prevalence of anaemia, leucopenia and thrombocytopenia was 20.1, 6.7 and 6.0 per cent, respectively. Normocytic anaemia was present in 19 (14.2%) patients. There were no significant differences in the prevalence of anaemia, leucopenia and thrombocytopenia between the two groups. There were no correlations between the PTH levels and the leukocyte, haemoglobin or platelet values. Six to 12 months after the parathyroidectomy (PTX), 35.7 per cent of the patients with anaemia, 85.7 per cent of the patients with leucopenia and 100 per cent of the patients with thrombocytopenia had recovered.**

***Interpretation & conclusions*: In the present study, anaemia was seen with a variable frequency in PHPT, but there was no relationship between anaemia and high PTH or Ca levels. The development of anaemia can be seen regardless of the PTH levels in PHPT patients with normal renal functions. High-resolution rates after PTX indicate a possible association between PHPT and thrombocytopenia or leucopenia, although their prevalence is low in PHPT.**

Key words Anaemia - haematological manifestations of systemic diseases - leucopenia - primary hyperparathyroidism - thrombocytopenia

Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused by the elevated secretion of the parathormone (PTH), and it occurs more frequently in women (3:1 ratio)[1,2]. A solitary parathyroid adenoma is the cause of PHPT in approximately 85 per cent of the patients[2]. The hypercalcaemia caused by the increased PTH is reportedly responsible for the clinical symptoms of PHPT[1,2].

There are several studies regarding haematological manifestations of PHPT. Anaemia was first reported as a complication of PHPT in the 1930s[3,4]. The reported prevalence of anaemia in PHPT cases has ranged

between five and 31.8 per cent in various studies before the 1990s[5-7]. However, a study published in 2009[8], reported that this prevalence was as high as 50 per cent. In PHPT cases, the anaemia is normocytic normochromic anaemia, which is a characteristic of chronic disease[3-8].

Thrombocytopenia, as a manifestation of PHPT, was first described in the literature in 2012 by Bhadada *et al*[9] and then in 2017 by De Keukeleire *et al*[10]. It is to note that in both the cases, the reversal of thrombocytopenia were reported after parathyroidectomy (PTX).

The aim of this study was to evaluate the haematological manifestations of PHPT. Furthermore, this study was aimed to include a larger sample size as compared to those published in literature evaluating the frequency of haematological findings in PHPT patients surgically treated for parathyroid adenoma with normal renal function.

Material & Methods

The medical records of all the patients with hyperparathyroidism who underwent surgery for parathyroid adenomas at the division of General Surgery, Ondokuz Mayıs University Hospital in Samsun, Turkey, from 2010 to 2018 were retrospectively reviewed in this study. The diagnoses were surgically and histologically proven, and all the patients were operated upon by the same surgical team.

This study was approved by the Institutional Ethics Committee of Ondokuz Mayıs University and has been performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The patients consented to these investigations as part of their normal medical care. We collected the details regarding the demographic data, medical histories, histological examinations, laboratory studies and imaging from the database records of our hospital.

Patient selection: A total of 217 participants were considered for the study, who were treated by PTX. Of these 83 of them were excluded. In total, 134 patients who were older than 17 yr, with complete medical records, a full patient history, physical examination results and biochemical values for the total serum calcium (Ca), serum creatinine (Cr), serum intact PTH and complete blood count (CBC) before the PTX were included in this study. Those patients with diagnoses of multiple endocrine neoplasia type 1 and 2 or any active malignancy (including thyroid or parathyroid malignancies diagnosed during the PTX), moderate-advanced chronic renal failure and thyroid or hepatic dysfunction were excluded.

The laboratory results of the patients were evaluated preoperatively and at the first follow up 6-12 months after the PTX. One of the indications for the operation (indicator of the severity of the disease) of a PHPT patient was that Ca level was 1 mg/dl above normal (11.2 mg/dl). So, the patients were divided into two groups according to their serum Ca levels (Group 1 $\leq$11.2 mg/dl and Group 2 >11.2 mg/dl), and the haematological presentations were evaluated between the groups.

Biochemical evaluation: The biochemical values of the serum Ca and serum Cr were measured using colorimetric and spectrophotometric methods with the cobas® 8000 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany); the reference range (RR) was 8.8-10.2 mg/dl for Ca and 0.4-1.4 mg/dl for Cr, respectively. The serum intact PTH level was measured using an electrochemiluminescence immunoassay with a Modular E170 analyser (Roche Diagnostics GmbH, Mannheim, Germany); the RR was 15-65 pg/ml.

The CBC included the white blood cell (WBC) count, haemoglobin (Hb) level, mean corpuscular volume (MCV), mean corpuscular Hb (HCH) concentration, red cell distribution width, platelet (PLT) count and mean platelet volume (MPV). These were all obtained by using electrical impedance with an LH 750 haematology analyser (Beckman Coulter Inc., Diagnostics Division, Brea, CA, USA).

In the absence of other aetiologies, hypercalcaemia and an elevated or inappropriately normal PTH level is typically diagnosed as PHPT[1]. Anaemia, thrombocytopenia and leucopenia were defined as having a Hb level of <12 g/dl for females and <13 g/dl for males. A WBC count of $<4.6 \times 10^9$/l and a PLT count of $<150\times10^9$/l, respectively. Polycythaemia, thrombocytosis and leucocytosis were defined as having a Hb level of >15 g/dl for the females and >17 g/dl for the males, a WBC count of $>11\times10^9$/l and PLT count of $>400 \times10^9$/l, respectively.

Statistical analysis: The continuous variables were tested for a normal distribution by Shapiro–Wilk test and the results were expressed as the mean±standard deviation only upon confirmation, otherwise, as median

Table I. Laboratory parameters of the study group

Study parameters	RR	Mean±SD	Median (IQR)	Minimum	Maximum
Age (yr)	>17	52.5±12.7	53 (17)	23	76
Creatinine (mg/dl)	0.4-1.4	0.71±0.18	0.67 (0.2)	0.38	1.4
Ca (mg/dl)	8.8-10.2	11.3±0.64	11.2 (0.7)	9.9	13.1
PTH (pg/ml)	15-65	219.7±172.1	162.1 (122.8)	65	1102
WBC ($\times 10^9$/l)	4.5-11	6.7±1.75	6.6 (2.3)	3.4	14.6
Hb (g/dl)	12-15 (F)	13.0±1.23	13.0 (2.1)	10.1	15.5
	13-17 (M)	15.0±1.41	15.3 (2.4)	12.8	17.5
Haematocrit (%)	35-45	40.5±3.8	40.3 (5.1)	32.5	53.7
MCV (fl)	80-94	87.4±5.7	87.75 (7.45)	66.6	100.4
PLT ($\times 10^9$/l)	150-400	265±78.4	252 (75.5)	89	689
MPV (fl)	7-11	8.3±1.1	8.2 (1.4)	5.9	12.0

SD, standard deviation; IQR, interquartile range; Ca, serum calcium; PTH, parathyroid hormone; WBC, white blood cell; Hb, haemoglobin; MCV, mean corpuscular volume; PLT, platelet; MPV, mean platelet volume

and interquartile range. The categorical variables were expressed as percentages. For the comparison of the categorical variables amongst the groups, Pearson's chi-squared test was used. For the comparisons of parameters, Pearson's chi-squared test was done by grouping the normal and abnormal values (low+high values grouped together). Spearman's correlation coefficient was used to assess the relationships between the continuous variables. IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. $P \leq 0.05$ was considered as statistically significant.

Results

This study included 134 participants (86.6% of females). The age of the patients was 52.5±12.7 yr. The Hb level was 13.0±1.23 g/dl for females and 15.0±1.41 g/dl for males. The study group's laboratory parameters are shown in Table I. The prevalence of anaemia, leucopenia and thrombocytopenia was 20.1, 6.7 and 6.0 per cent, respectively (Table II). Normocytic anaemia was present in 19 (14.2%) of the patients.

The study participants were divided into two groups according to their serum Ca levels (Group 1 ≤11.2 mg/dl and Group 2 >11.2 mg/dl). There was no significant difference based on gender between the two groups (P=0.477). The prevalence of leucopenia, anaemia and thrombocytopenia was 5.7, 25.7 and 7.1 per cent, respectively, in Group 1 and 7.8, 14.1 and 4.7 per cent, respectively, in Group 2. There were no significant differences between Group 1 and Group 2 in the WBC, Hb, MCV, MPV and PLT values (P=0.271, P=0.051, P=0.08, P=0.304 and P=0.928, respectively) (Table II). The laboratory parameters of the normocytic anaemia subgroup are shown in Table III.

In Spearman's correlation analysis, the PTH level was not found to correlate with the WBC, Hb or PLT values across the study groups (P=0.441, P=0.894 and P=0.219, respectively).

The laboratory parameters were re-evaluated 6-12 months after the PTX, and of the 19 normocytic anaemia patients, five of them recovered, nine were unchanged and five did not show up for the follow up. Five of the eight thrombocytopenic patients recovered and three of them did not show up for the follow up. Of the nine leucopenia patients, six recovered, one was unchanged and two did not show up for the follow up. None of the normocytic anaemia cases were associated with leucopenia; however, one thrombocytopenic participant also had normocytic anaemia. Both the anaemia and thrombocytopenia was, however, resolved in this participant during the post-PTX period.

Discussion

Haematological manifestations, such as anaemia, leucopenia and thrombocytopenia, are less known in PHPT. To our knowledge, this is so far the first study to examine the haematological presentations in PHPT patients surgically treated for parathyroid adenomas with normal renal functions.

Anaemia was first reported as a complication of PHPT in the 1930s[3,4], and it was seen in five to 31 per

Table II. Biochemical and biometric characteristics of the patients according to their calcium levels

Study parameters	RR	Group 1 (Ca≤11.2) (n=70), n (%)	Group 2 (Ca>11.2) (n=64), n (%)	Total (n=134), n (%)
Sex				
Female	-	62 (88.6)	54 (84.4)	116 (86.6)
WBC (×10⁹/l)				
Leucopenia	<4.5	4 (5.7)	5 (7.8)	9 (6.7)
Normal	4.5-11	66 (94.3)	57 (89.1)	123 (91.8)
Leucocytosis	>11	0	2 (3.1)	2 (1.5)
Hb (g/dl)				
Anaemia	F<12 M<13	18 (25.7)	9 (14.1)	27 (20.1)
Normal	12-15 F 13-17 M	49 (70)	54 (84.4)	103 (76.9)
Polycythaemia	F>15 M>17	3 (4.3)	1 (1.6)	4 (3.0)
MCV (fl)				
Low	<80	9 (12.9)	2 (3.1)	11 (8.2)
Normal	80-94	53 (75.7)	56 (87.5)	109 (81.3)
High	>94	8 (11.4)	6 (9.4)	14 (10.4)
MPV (fl)				
Low	<7	9 (12.9)	6 (9.4)	15 (11.2)
Normal	7-11	58 (82.9)	57 (89.1)	115 (85.8)
High	>11	3 (4.3)	1 (1.6)	4 (3.0)
PLT (×10⁹/l)				
Thrombocytopenia	<150	5 (7.1)	3 (4.7)	8 (6.0)
Normal	150-400	62 (88.6)	57 (89.1)	119 (88.8)
Thrombocytosis	>400	3 (4.3)	4 (6.3)	7 (5.2)

RR, reference range

Table III. Laboratory parameters of the normocytic anaemia subgroup

Study parameters	RR	n	Mean±SD*	Minimum	Maximum
Age (yr)	>17	19	51.3±12.3	29	72
Ca (mg/dl)	8.8-10.2	19	11.2±0.6	10.2	12.6
PTH (pg/ml)	15-65	19	211.7±112.5	65.8	492.1
Hb (g/dl)	12-15 (F)	18	11.5±0.6	10.1	12.8
	13-17 (M)	1			
Haematocrit (%)	35-45	19	36.3±2.1	32.5	41.1
MCV (fl)	80-94	19	84.7±3.5	80.1	91.4
MCHC (g/dl)	31.8-35.9	19	32.4±0.8	31.2	34.7
RDW (%)	11.3-14.7	19	14.2±0.6	12.7	14.7

*Expressed as mean±SD because of normal distribution. RDW, red cell distribution width

cent of patients with PHPT. Furthermore, it was found to be predominantly normocytic anaemia[5-7]. Bhadada *et al*[8] evaluated 28 symptomatic patients with PHPT and found 53.3 per cent of these were anaemic. Of these 50 per cent had normocytic anaemia. These were higher prevalence rates at the time than those previously reported[5-7]. In

the present study, anaemia was observed in 27 (20.1%) of the 134 patients but normocytic anaemia, which is characteristic of PHPT, was found only in 19 (14.2%) of the patients. Such differences between the incidences of anaemia in PHPT patients may be due to studies conducted in different societies and early diagnosis of patients which may be the reason for the considerably lower incidence of anaemia in the present study than Bhadada *et al*[8]. A multicentre study[9] from India in 2017, demonstrated greater severity among long-term PHPT patients. Furthermore, in most studies, the frequency was given without investigating the aetiology of anaemia. None of these studies evaluated iron, folic acid and vitamin B12 levels but excluded these aetiologies of anaemia based on patient history. Finally, the symptomatic status of the patients was different in the studies.

It is likely that the pathogenesis of anaemia in PHPT is multifactorial. Previously, it was reported that bone marrow fibrosis may be the cause[5,10,11]. The elevated PTH levels are likely to be related to bone marrow fibrosis[10-13]. The induction of certain cytokines, such as interleukin-6 and tumour necrosis factor is also thought to be the alternate mechanism due to the elevated PTH levels[5,14,15]. Some studies have demonstrated that intact PTH has inhibitory effects on the growth of erythroid progenitor cells and erythropoietin synthesis[16,17]. However, this was contradicted by another study[18] as a result, the role and mechanism of PTH on anaemia development are controversial. Furthermore, no such relationship was reported by Bhadada *et al*[8].

Moreover, no correlation was found between the PTH levels and the Hb, WBC or PLT levels in the present study. Also, correlation between anaemia and/or bone marrow fibrosis in PHPT and the disease duration, hypercalcaemia degree and 25-hydroxyvitamin D levels were reported by some studies[5,19,20], but not in others[7,8]. Thus, bone marrow fibrosis may be a major factor, but not the only factor contributing to anaemia development in PHPT. However, the improvements in anaemia[5,6,8,10,17,19,21] and bone marrow fibrosis[8,10,17,19] after a PTX are in a way suggestive of marrow fibrosis due to PHPT.

A 10 yr follow up after surgery showed no anaemia among eight patients[22]. Upon analysis of the results of our study with follow up laboratory values 6-12 months post-PTX, 35.7 per cent of the patients with anaemia, 85.7 per cent with leucopenia and 100 per cent of the patients with thrombocytopenia had recovered.

In our study group, the rate of anaemia was not high and only one-third of the patients recovered after surgery. Persistent bone marrow fibrosis or other undiagnosed anaemia aetiologies may be the cause of unresolved anaemia. Most of the studies evaluating the relationship between hyperparathyroidism, anaemia and bone marrow fibrosis included patients with renal failure in their respective studies[10-12,20]. The mechanism of anaemia development in hyperparathyroid patients with renal failure in these studies may, however, be different than in PHPT patients with normal renal functions, as in our study.

In our study, the prevalence of leucopenia and thrombocytopenia was 6.7 and six per cent, respectively, and no relationship was found between the co-occurrence of normocytic anaemia and leucopenia or thrombocytopenia. Only two cases of reversible thrombocytopenia have been reported previously in the literature[23,24]. Moreover, Boxer *et al*[5] reported that leucopenia and thrombocytopenia were not encountered in any of their study subjects. The underlying mechanism for thrombocytopenia development in PHPT patients is also unknown. PTH-promoted bone marrow fibrosis can be a cause of thrombocytopenia by causing a decrease in the haematopoietic elements, and the thrombocytopenia improvement post-PTX supports this[23,24]. There have been no previous studies reporting leucopenia in PHPT; therefore, this is the first study reporting leucopenia in 6.7 per cent of the PHPT patients, with a high rate of resolution after the PTX.

Despite this, our study did have some limitations. Because this was retrospective, the post-operative values of some of the patients could not be obtained. Therefore, we were unable to fully assess the cytopenia correction rates in those patients. Further prospective studies can be planned to elucidate the aetiology of unresolved cytopenia including bone marrow evaluation on more patients.

In conclusion, anaemia is seen in PHPT patients with a variable frequency. When we evaluated the parameters affecting the Hb levels, no relationship was found between anaemia and high PTH and Ca levels. The development of anaemia, likely due to bone marrow fibrosis, can be seen independently of the PTH levels in PHPT patients with normal renal functions. High-resolution rates after PTX indicate a possible association between PHPT and thrombocytopenia or leucopenia, although their prevalence is low in PHPT.

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Conflicts of Interest**:** None.

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