REVIEW ARTICLE

The Hematology of Anorexia Nervosa

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ABSTRACT

Objective: Changes of the peripheral blood cell count in patients with anorexia nervosa (AN) are frequent. Anemia and leukopenia are observed in one-third of these patients. Examination of the bone marrow reveals in almost 50% of the patients with AN signs of bone marrow atrophy and can additionally suffer from a gelatinous bone marrow transformation.

Method: Published studies and investigations concerning hematological changes in patients with AN were reviewed.

Results: Anemia and mild neutropenia are detectable in almost one-third of these patients, whereas thrombocytopenia is rather uncommon. The exact mechanism for these findings is still unclear, but 50% of AN-patients with hematological changes display morphological signs of partial bone marrow atrophy.

Discussion: Changes of the peripheral blood cell count in patients with AN is a frequent observation but the peripheral blood cell count cannot predict the severity of bone marrow atrophy. All hematological and morphological alterations disappear completely and rapidly after sufficient refeeding. © 2008 by Wiley Periodicals, Inc.

Keywords: anorexia nervosa; GMT; bone marrow transformation

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Introduction

Anorexia nervosa (AN) is an eating disorder with a prevalence of ~0.5–1% of all adolescents.[1–3] With regard to other psychiatric disorders, AN is associated with the highest mortality rate. Suicide and cardiovascular events are the most important reasons for fatalities during the course of the disease.[4] Other well-known significant comorbidities are weakness, dizziness, fatigue, or amenorrhea.

Routinely performed laboratory tests often reveal mild alterations of the total blood cell count. However, dramatic changes can occur, mimicking a severe hematological disease such as acute leukemia or idiopathic thrombocytopenia. Examination of the bone marrow aspirate frequently displays signs of hypoplasia and, more rarely, a complete atrophic transformation with the deposition of an amorphous material, designated as "gelatinous transformation" (GMT).

In this review, features and frequency of the hematological characteristics in patients with AN are summarized and several options concerning diagnostic and therapy are discussed.

Disturbances of the Erythropoiesis

Hemoglobin

Anemia, defined as reproducibly low hemoglobin level less than 14 g/dl in men or 12 g/dl in women, is a common observation in patients with malnutrition. The incidence rate of anemia in patients with AN varies from 21 to 39% (Table 1). The majority of epidemiological data was collected throughout clinical findings of in-patients who suffered from a worse nutrition status or complications due to an eating disorder. There is only one trial focusing on the incidence rate in out-patients. However, mild anemia is present in one-third of all patients suffering from AN.

Characteristically, the mean corpuscular hemoglobin (MCH) and the mean corpuscular volume (MCV) are normal.[10] Furthermore, a case–control study of patients with AN found normal but significantly higher values for MCV and MCH in AN-patients in comparison to a control-group consisting of healthy individuals (Table 2).[13] Anemia with elevated MCV or MHC without a lack of folic acid

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TABLE 1. Frequency of the observed hematological changes in total blood cell count according to five trials with more than 30 patients

	Palla 1988[5]	Devuyst 1993[6]	Alvin 1993[7]	Abella 2002[8]	Miller 2005[9]
Number of patients	38[a]	67[a]	92[a]	44[a]	214[b]
Age in years (range)	15.3 (11–19)	22.4 ± 6 (NR)	16.6 ± 2.1 (11.8–22.0)	22 ± 5.3 (13–38)	25 ± 6.4 (17–45)
BMI in (kg/m^2)	NR	14 ± 2	NR	NR	16.8 ± 1.4
Duration of AN in months (range)	10.8 (2–36)	NR	NR	NR	65 ± 70.4 (1–336)
Frequency of anemia	34%	27%	21%	34%	39%
Frequency of leukocytopenia	29%	36%	29%	29.5%	34%
Frequency of thrombocytopenia	NR	10%	5%	11.3%	5%

Notes: Anemia was defined as hemoglobin < 12.0 g/dl, leukocytopenia < 4.5 /nl, thrombocytopenia < 150 /nl. NR, not reported; AN, anorexia nervosa.
[a] In-patients.
[b] Out-patients.

TABLE 2. Summary of trials investigating hematological changes of patients with anorexia nervosa in comparison to a control group (squared bracket)

	Devuyst 1993[6]	Lambert 1997[11]	Nagata 1999[12]	Misra 2004[13]
No. of patients	67 [67]	10 [19]	17 [17]	60 [58]
BMI in (kg/m^2)	14.0 ± 2 [22.0 ± 4.0]**	14.0 ± 0.5 [22.3 ± 0.4]**	11.6 ± 1.3 [20.1 ± 1.3]**	16.6 ± 1.4 [21.8 ± 3.6]**
RBC in ($\times x10^{12}/l$)	NR	NR	3.4 ± 0.5 [4.3 ± 0.3]*	4.3 ± 0.3 [4.5 ± 0.3]*
Hb in (g/dl)	13.1 ± 1.9 [13.7 ± 1.1]*	13.0 ± 0.1 [13.5 ± 0.2]***	NR	NR
MCV in (fl)	NR	NR	NR	88.2 ± 3.5 [84.7 ± 4.6]**
MCH in (pg)	NR	NR	NR	30.6 ± 1.4 [29.1 ± 1.7]**
MCHC in (g/dl)	NR	NR	NR	34.7 ± 1.0 [34.4 ± 1.0]***
WBC in ($10^9/l$)	4.9 ± 1.9 [6.7 ± 2.4]**	4.5 ± 0.4 [6.3 ± 0.3]**	3.5 ± 0.9 [5.7 ± 1.1]***	5.4 ± 1.1 [7.4 ± 1.9]**
Lymphocytes in ($10^9/l$)	1.7 ± 0.7 [2.0 ± 0.6]*	1.6 ± 0.1 [1.8 ± 0.1]***	1.3 ± 0.4 [2.0 ± 0.5]***	NR
Monocytes in ($10^9/l$)	0.2 ± 0.1 [0.3 ± 0.1]**	0.24 ± 0.03 [0.37 ± 0.03]*	0.15 ± 0.08 [0.2 ± 0.1]***	NR
Neutrophils in ($10^9/l$)	2.8 ± 1.5 [4.1 ± 1.9]**	2.4 ± 0.3 [3.7 ± 0.2]**	1.9 ± 0.6 [3.2 ± 0.9]***	NR
Platelet count in ($10^9/l$)	240 ± 86 [261 ± 50]*	184 ± 17 [238 ± 9]**	NR	244 ± 47 [262 ± 66]***

Notes: Statistical analysis was performed using an unpaired *t*-test. NR, not reported.
* $p < .05$, ** $p < .001$, *** not significant.

or vitamin B12 is a rare constellation in patients with AN.[14]

There are only few investigations focusing on the plasma volume in severely malnourished patients. In a study of 14 patients with AN, the measurement of plasma volume using the urea nitrogen/creatinine-ratio revealed that the depletion of plasma volume concealed the severity of an anemia in 64% of these patients. Caregaro et al.[15] assumed that the plasma volume concentration is a consequence of extracellular volume depletion, due to salt and water deficits caused by the malnutrition.

At present, the pathophysiological reasons of an anemia in AN are not clarified in detail yet. Most authors agree upon the theory that the lack in the red cell production corresponds to morphological changes in the bone marrow. On the other side, there are several cases of anemia without any morphological impairment of the bone marrow. Furthermore, it is certain that anemia is not associated with a lack of serum ferritin, vitamins, or erythropoietin.

Red Blood Cell Morphology

The most frequent morphologic alterations of red blood cells in peripheral blood in patients with AN are anisocytosis, poikilocytosis, and occasionally acanthocytosis.[10] Acanthocytes, which are commonly observed in patients with congenital abetalipoproteinemia, are characterized by the presence of irregularly shaped external projections distributed unevenly at the membrane surface. The exact mechanism of this phenomenon is poorly understood but it is suggested that a disturbance of the Band 3 anion exchange protein is responsible for this occurrence.[16] Although fat intake is reduced, and the serum level of lipoproteins is usually normal or elevated in patients with AN, some of them develop a lipid profile similar to patients with abetalipoproteinemia. The mechanism of this finding is currently unsolved and three possible reasons are therefore discussed: (1) depletion of hepatic substrate for synthesis of apolipoprotein B, (2) lack of exogenous fatty acid with exhaustion of endogenous stores, and (3) preservation of the

lipoprotein lipase mass. This theory is supported by the observation that acanthocytosis rapidly disappears during the refeeding process.[17,18]

Hemolytic Anemia

An acquired hemolytic syndrome was reported in a patient suffering from AN and hypophosphatemia.[19] Hypophosphatemia accompanying AN is a potentially life-threatening complication during the refeeding process.[20] The increased caloric intake leads to a consecutive relative hyperinsulinism. Thereby a shift of phosphate into muscle and liver cells is presumed to cause the hypophosphatemia.[21] During severe hypophosphatemia erythrocytes run out of ATP, which is essentially needed to maintain the integrity of the cell membrane and, as a consequence, this disturbance leads to the observed hemolysis. Therefore, serum levels of phosphate during the initial feeding program should be monitored regularly.

Reticulocytes

The number of reticulocytes is a good indicator for bone marrow activity. According to the assumption that anemia in patients with AN is caused by a reduced red cell production, the count of reticulocytes is normal or decreased. The investigations concerning this aspect of hematopoiesis are somewhat casuistic.[10] Kubanek investigated a small group of nine AN-patients with neutropenia or thrombocytopenia as an indicator for bone marrow affection. After all, 44% of the patients had a reduced count of reticulocytes although hemoglobin level was in normal range.[22]

Iron Metabolism

Iron deficiency is not a typical finding in patients with AN, especially not in female patients. This is most likely due to the frequent occurrence of secondary amenorrhoea resulting in a reduced iron loss in these patients. A systematic study of the iron physiology in patients with AN was performed by Kennedy et al. who generally found a normal serum iron concentration and ferritin level. Surprisingly, 33% of the patients demonstrated an elevated level of serum ferritin, decreasing to a normal range after refeeding. The authors presume that there is increased iron storage as a secondary consequence of the diminution of circulating blood during malnutrition which results in elevated ferritin levels. Furthermore, after refeeding, the blood volume and red cell mass restores with weight gain.[23]

Erythropoietin

The erythropoietin level in patients with AN is typically within the normal range. During the refeeding process this hormone increases significantly with the growth of weight.[24] To accelerate the recovery from anemia some authors postulate the administration of exogenous erythropoietin. Initial hormone doses of 3000 units (U) per day for 10 days followed by 2000 U twice a week over a period of 4–6 weeks were found to be sufficient to reach normalization of the hemoglobin level.[25]

Disturbances in the Leukopoiesis

Granulocytes

Although leukocytopenia can be observed in 29–36% of the patients with AN, severe cytopenias with a granolucyte count below 0.5/nl are rather uncommon (Table 1).[7,19,26] Leukocytopenia is more frequent in AN-patients who are strict dieters than in those who vomit or purge (36% vs. 10%).[5] There are two studies with contradicting results investigating the correlation of total body mass fat (assessed by dual energy X-ray absorptiometry) and white blood cell (WBC) count. Although Lambert et al. found a relationship between total body mass fat and the leukocyte count, Misra et al. were not able to confirm this observation. Nevertheless several trials revealed a strong correlation between duration of illness and severity of WBC cytopenia.[6,13,27]

Lymphocytes

Analysis of the differential blood cell count reveals a significant lymphocytopenia in patients with AN.[28] In a two case–control trial, the lymphocyte subset in anorectic patients was investigated and compared with a healthy control group. There was no affection of the total T- and B-lymphocytes proportions. Both studies found a considerable alteration of T-cell subpopulations. Although memory T-cell (CD4/CD45RO+) and CD8 T-cells were overexpressed, there was a reduction of the naÿve CD4/CD45RA+ population leading to an increased CD4/CD8 ratio correlating significantly with the BMI and total blood protein levels. Nagata and et al. concluded that the cell-mediated immunity was impaired and suggested that the high CD4/CD8 ratio is a compensatory mechanism. Furthermore, the presence of memory T-cells might explain the absence or minor risk for severe infections.[12,29]

Paszthy performed a study with 21 AN-patients to determine how malnutrition may influence the

count of regulatory T-cells and their cellular networks and compared the data with a control group of healthy, aged-matched individuals. By means of an in vitro assay he could demonstrate that the antigen presenting axis of the regulatory T-cells, including dendritic cells, tumor necrosis factor (TNF)-alpha and IL-12-positive monocytes, and IL-4 and interferon (IFN)-γ-producing CD4+ cells, was not affected.[30] In contrast to this in vitro observation, investigations of the cell-mediated immunity in terms of delayed hypersensitivity revealed a reduced cutaneous reaction in patients with AN.[31]

Cytokine Induction and Lymphocyte Activation

The balance between immunomodulatory mediators and the capacity of T-lymphocytes to respond to these factors is an important element in the process of T-cell activation. However, this course is complex and because of high interindividual variations, the interpretation of observed alterations remains difficult.[32] Several studies, investigating the cytokine production of patients with AN were performed, but the results are controversial.[33] A number of studies investigated serum levels of IL-1, IL-4, IL-6, IL-10, TNF-α, or interferon (IFN)-γ but could not observe a significant difference in patients with AN compared with a matched control group. In some studies, AN-patients had significant lower levels of IL-2 and TGF-β2, whereas in another study, AN-patients had normal levels of IL-2 but a significant lower capacity to synthesize IL-2 in comparison to the control group.[34–37]

Some authors suggest a role for TNF-α in the pathogenesis of AN. They argue that the causal interplay between the cytokines, neuropeptides, and neurotransmitters initiates a cascade of biochemical events which may result in either AN or bulimia nervosa, or cachexia caused by other illnesses like cancer.[36] Indeed, Allende et al.[29] found an elevated production of TNF-α in AN-patients compared with a control group. However, this observation was not reproducible and the presumed role of TNF-alpha in the development of AN still needs to be clarified.[37]

Despite of the contradicting results in the observed changes of cytokine production, there is common sense that the alterations quickly reconstitute to normal conditions after a successful refeeding procedure.[38,39]

Infectious Complications

Although it has been suggested that AN-patients are obviously less susceptible to infections in contrast to other protein-calorie malnourished individuals, a closer look on the infectious risk led to contradicting results.[40,41] In 1978 and 1993, two different retrospective case–control studies of 67 and 68 AE patients, respectively, were performed. In both studies, significant lower levels of leukocyte count compared with a stratified control group were found. Devuyst et al. found a significantly increased risk for severe infectious events in the AN-patient group, clinically impressing as pneumonia ($n = 4$) and septicemia ($n = 2$). During time of infection all six patients had low leukocyte counts. Four of the six had a count of neutrophils between 1.0 and 1.3 $\times$ 10^9/l but all six patients had a very low body mass index (BMI). Furthermore, some patients with neutropenia received an additional medication of hydrocortisone resulting in an adequate increase of leukocyte count demonstrating an adequate bone marrow function.[6] In conclusion, the combination of a relevant leukopenia and a low BMI, indicating a bad performance status, may lead to an increased risk of infectious complications.

Although only few data exist concerning the evaluation of serum level of G-CSF in patients with AN, all measurements displayed normal serum level for this cytokine.[42] In a case report of a patient with AN and severe neutropenic fever and gangrenous stomatitis, the administration of G-CSF rapidly reversed the leukopenia. After combined antibiotic therapy as well as careful nutrition the patient recovered from this infectious complication.[43]

Disturbances of the Thrombopoiesis

The incidence of thrombocytopenia in patients with AN ranges between 5 and 11%. The platelet count is slightly reduced between 90 $\times$ 10^9 and 130 $\times$ 10^9/l (Table 1).[19,26] Platelet counts below this value are rather uncommon but in contrast to other diseases with severe thrombocytopenia (e.g., aplastic anemia or idiopathic thrombocytopenia) the hemorrhagic tendency in patients with AN appears more frequently. It is supposed that other factors, such as increased fragility of blood vessels, may be superimposed.[44] Because of the low incidence of very severe thrombocytopenias, reports of bleeding complications are casuistic. Thrombocytopenia in AN-patients can easily be managed using platelet packs. According to the previously described hematological findings in AN-patients, there is a possible correlation between thrombocytopenia and the duration of the eating disorder with consecutive rapid

TABLE 3. Summary of all case reports of patients with anorexia nervosa and gelatinous bone marrow transformation during the last 25 years

Year	Gender	Age	BMI in (kg/m^2)	Leukozytes in (10^9/l)	Hemoglobin in (g/dl)	Platelets in /(10^9/l)	Reference
1990	F	15	8.7	2.1	8.5	62	51
1992	F	50	12.2	1.6	12.6	247	52
1994	F	20	11.1	2.7	10.6	208	53
1995	F	29	12.0	1.5	9.4	354	14
1995	F	25	14.0	2.6	8.5	200	54
1995	F	18	12	NR	10.2	80	54
1995	F	48	11.0	4.4	3.6	323	54
1999	F	18	10.1	3.8	15.6	49	44
1999	F	16	10.4	4.7	14.5	74	44
1999	F	14	11.1	8.9	13.2	7	44
2000	F	27	11.3	2.7	9.6	134	25
2001	F	37	18.5	2.2	11.9	172	55
2003	F	28	12.3	0.9	8.8	115	42
2004	M	28	18.0	2.4	11.8	97	56
2004	F	30	12.5	1.33	13.1	345	57
2005	F	28	12.2	1.5	8.8	112	58
2007	F	26	11.3	1.7	10.9	>150	59

Notes: Anemia was present in 78%, leukocytopenia in 66%, and thrombocytopenia in 46%.

reversibility of the condition with the refeeding process.[19]

Bone Marrow Hypoplasia and Gelatinous Transformation

Morphologic changes in the bone marrow, combining an atrophy of fat cells and a loss of hematopoietic cells with the deposition of an amorphous gelatinous material, has been described as "gelatinous transformation" (GMT) or "serous atrophy." For diagnosis bone marrow aspirate is feasible but bone marrow biopsy remains as the gold standard. The spectrum of underlying diseases in Western Europe and North America leading to GMT are in 37.5% tumors, in 16.8% malnutrition, and in 11.8% infections.[45,46] The gelatinous material can be stained according to the May-Grünwald protocol. It shows a weak positive PAS-reaction and is stainable with alcian blue at ph 2.5 in contrast to the ground substance. Immunohistochemical studies defined this substance as hyaluronic acid.[47] Most of the GMT lesions were focal and in severe cases, the number of hematopoietic as well as fat cells, was dramatically reduced and empty spaces were filled with the gelatinous material.[48] An overview of the appearance of GMT is given in the image bank of the American Society of Hematology (http://ashimagebank.hematologylibrary.org/). These bone marrow findings reflect the consequences of the unusual malnutrition in AN-patients, mainly appearing as a deficiency of carbohydrates and calories, which represent the source of marrow fat. Bone marrow hypoplasia without accumulation of gelatinous material occurs in other starvation states, such as marasmus or kwashiorkor, where protein is the dietary deficiency.[49] In fact, the exact pathophysiological mechanism of this feature of bone marrow atrophy remains unresolved. Morphological studies revealed an increase in the fat fraction and a relative increase in the size and number of adipocytes in the bone marrow in AN-patients leading to a partial reduction of normal hematopoietic tissue. Finally, the collapse of the adipocytic tissue and the filling of the free spaces with hyaluronic acid, leads to the characteristic picture of GMT.[48]

The first cases of GMT in patients with AN were reported in 1967 by Pearson[50] The frequency of occurrence of GMT was investigated by Warren and et al. They found signs of bone marrow hypoplasia in 46% of AN-patients who already showed alterations of their total blood count.[26] Abella et al. performed a study of bone marrow aspirates in 44 patients with AN without changes in the total blood cell count. Samples were classified according to histological patterns into normal, aplastic or hypoplastic, pre-GMT, and GMT. They found an excellent correlation between cytological and histological results and suggested that a bone marrow aspirate alone would be sufficient to assess the bone marrow status in these patients. Peripheral blood cytopenias tended to appear more often in patients with evidence of GMT. Table 3 gives an overview of the changes of peripheral blood cell count in case reports of GMT in patients with anorexia nervosa. Furthermore, ~50% of the patients with a normal blood cell count had signs of bone marrow atrophy. Therefore, a normal peripheral

blood count is not a reliable predictor for the degree of bone marrow impairment.[8]

Some authors found a correlation between the duration of AN and the development of bone marrow hypoplasia but most of the studies revealed a correlation between bone marrow transformation and reduced total fat mass index.[6,11,13,27] However, the minimal time of malnutrition that leads to GMT is still unknown. Wang et al. reported from a 25-year-old man without AN, who suffered from Type I diabetes mellitus. For a period of 6 months this patient underwent an extreme starch-free diet. Although weight loss was only 4 kg during this time, the patient developed a pancytopenia with GMT similar to patients with AN.[60]

On the other side, there are several reports of rapid reversal of bone marrow transformation during refeeding. Steinberg published a case of severe GMT with pancytopenia. After intensive nutritional support for 2 weeks the peripheral blood count had returned to normal. Unfortunately, this patient died 2 weeks later but the autopsy revealed a normal bone marrow morphology.[61]

For diagnosis of GMT, bone marrow aspirate is the standard investigation. The distribution of GMT was investigated using T1- and T2-weighted magnetic resonance (MR) images. In the lower limbs, marrow changes predominate in the distal parts. This distribution is similar to the normal distribution of hematopoietic to fatty marrow.[49,62] The ^{1}H-NMR spectrometric relaxometry is a technique allowing quantification of the proportion of fat and the content of interstitial tissue water in the bone marrow. In AN-patients, a reduction of fat, predominantly in the marrow of the femur epiphysis, can be observed. There was only a weak correlation between MR marrow measurements and BMI. Furthermore, duration of illness, type of anorexia, and other psychological symptoms measured by the SCL-9-R (General Symptom Index and subscales) could not be aligned with MR variables. A low leukocyte count was associated with reduction of fat in the femur epiphysis and anemia was associated with elevated T2 time only in cases with very severe morphological bone marrow changes.[63]

Summary

Changes of the peripheral blood cell count in patients with AN is a frequent observation, revealing that almost one third of them suffer from anemia or neutropenia and 5–10% from thrombocytopenia. Anemia is characterized by normal values for MCV and MCH, as well as for ferritin, folic acid and vitamin B12. The severity of anemia can be masked by sodium depletion and hemoconcentration due to purging or vomiting.

Mild leukocytopenia is rather common but there is no significant evidence between the severity of leukopenia and an increased risk of infectious complications for AN-patients. Severe neutropenia is rather uncommon and, if necessary, rapidly reversible through administration of exogenous G-CSF. Probably the combination of severe neutropenia and bad performance status is associated with a higher incidence of infectious complications. Nevertheless there are measurable alterations in the T- and B-cell mediated immunity, but there is no evidence of an increased risk for opportunistic infections.

The platelet production is sufficient to maintain a normal coagulation, and severe thrombocytopenias with episodes of bleeding are rare.

Bone marrow atrophy and gelatinous transformation are characteristic findings in patients with AN and they are more likely associated with body fat mass index than with duration of illness. It has been suggested that anorexia nervosa leads in half of the patients to an atrophy of the bone marrow. In fact, peripheral blood cell count cannot predict the severity of bone marrow atrophy, but interestingly 50% of patients with hematological changes in the peripheral blood count display morphological signs of a gelatinous transformation in the bone marrow aspirate. It is important to mention that all hematological and morphological alterations disappear completely and rapidly after sufficient refeeding.

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