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Case Report

The Impact of Body Weight Changes on the Hematologic Complications in Eating Disorders: A Case Report and Literature Review

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Abstract

Gelatinous marrow transformation (GMT) is a frequently encountered hematologic condition in those with malnutrition that results in reduced peripheral blood counts. Although malnutrition is frequently implicated as a contributor toward development of GMT, the nutritional impact toward its development and the associated reduced peripheral blood counts are poorly elucidated. Furthermore, the direct impact of nutritional rehabilitation toward resolution of this complication is not well researched. A case report of a malnourished woman whose anemia normalized solely due to weight restoration and a literature review of the hematological abnormalities associated with disordered eating are presented herein.

Keywords: Malnutrition; Treatment; Gelatinous Marrow Transformation; Anemia; Leukopenia

Abbreviations

AN: Anorexia Nervosa; AN-R: Anorexia Nervosa Restricting Subtype; BMI: Body Mass Index; ED: Eating Disorder; GMT: Gelatinous Marrow Transformation; WBC: White Blood Cell

Introduction

Medical complications from eating disorders (EDs) and other causes of malnutrition affect every body system [1]. The hematologic complications frequently include reduced peripheral blood counts and gelatinous marrow transformation (GMT). GMT, also known as serous fat atrophy or colloquially as starvation marrow, is a condition of marrow replacement with gelatinous substances identified histochemically as hyaluronic acid, along with fat atrophy, and loss/disappearance of the hematopoietic elements, resulting in decreased peripheral blood counts [2,3]. Although weight loss is a frequent contributor toward development of GMT, weight loss is not a prerequisite as not all patients with weight loss and cachexia develop GMT [4]. Indeed, Bohm (2000) found that among 69 patients with GMT from various causes and a documented body weight, only about three quarters had experienced severe weight loss [5].

In individuals with EDs, variable rates of leukopenia, anemia, and thrombocytopenia are found, typically dependent on the severity of the weight loss. In one cohort of patients with severe EDs with a mean body mass index (BMI) of 12.1 kg/m^2, 64% of individuals requiring inpatient care presented with leukopenia, 47% admitted with anemia, and 20% admitted with thrombocytopenia [6]. In another ED cohort, albeit less ill, with a mean BMI of 16.8 kg/m^2, 34.4% presented with leukopenia, 38.6% presented with anemia, and 5% had thrombocytopenia [7]. Similarly, an ED cohort with a mean BMI of 17.4 kg/m^2 demonstrated leukopenia in 50.5% of individuals with anorexia nervosa restricting subtype (AN-R), anemia in 16.4% of individuals with AN-R, and thrombocytopenia in 7.4% of people with AN-R [8]. Ultimately, the cause of the reduced blood counts remains to be elucidated, and although white blood cell counts tend to be lower in those with GMT, the severity of the reduced blood counts do not seem to correlate with the severity of the bone marrow changes [3-5,9].

A case report of a patient with self-inflicted starvation and critical anemia in the setting of presumed GMT follows. A literature re-

view of the hematologic abnormalities associated with disordered eating, and a focus on the nutritional impact on these complications, is thereafter presented.

Case Presentation

A woman in her early 40s was transferred via air ambulance from an outside hospital to an inpatient unit (ACUTE) that specializes in the medical stabilization of patients with severe malnutrition related to EDs and other causes. She had initially admitted to the outside hospital one month prior at 39.5 kg (height 5'4", body mass index (BMI) 14.9 kg/m^2) with concerns for an underlying ED. History was also significant for stage IIa invasive lobular breast carcinoma (cT3cN1, G2, ER+, PR+, HER2-) diagnosed eight months prior to admission to ACUTE, for which she had received two cycles of neoadjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel. This patient began self-starvation in parallel with the chemotherapy, believing the starvation would effectively cure her cancer. Her oral intake was further impacted by the effects of chemotherapy on her appetite, as she had developed increasing fears of gastrointestinal distress with any food intake. Additional chemotherapy had therefore been delayed due to significant weight loss and her continued decline in functional status.

On admission to the outside hospital, hemoglobin was initially found to be 11.3 g/dL (normal range: 12-16 g/dL) with a white blood cell (WBC) count of 2.6 k/uL (normal range: 4-10 k/uL) and normal liver function tests. Due to frequent refusal of prescribed nutrition, she was initiated on total parenteral nutrition; however, she continued to lose additional weight with development of elevated liver function tests, consistent with starvation hepatitis, and her hemoglobin continued to decline, reaching 6 g/dL the day prior to transfer to ACUTE. This patient was a Jehova's witness and had declined transfusion.

Upon arrival to ACUTE, her weight had further decreased to 36.3 kg (BMI 13.7 kg/m^2), temperature was 36.3 C, heart rate was 99 beats per minute, respiratory rate was 20 breaths per minute with 96% oxygen saturation, and blood pressure was 114/81 mm Hg. Exam revealed cachexia, dry mucous membranes, pale conjunctivae, significant sarcopenia with resultant weakness and bed-bound status, and a flat affect with delayed speech and cognition; however, there were no signs of active bleeding. Complete blood count revealed a WBC count of 1 k/uL, a hemoglobin of 5.4 g/dL, mean corpuscular volume (MCV) of 107.6 fL (normal range: 80-100 fL), and platelets of 181 k/uL (normal range: 150-400 k/uL), presumably due to GMT. A complete metabolic panel revealed normal electrolytes with ALT of 446 U/L (normal range: 7-45 U/L) and AST of 328 U/L (normal range: <40 U/L), as well as low total protein of 4.4 g/dL (normal range: 5.7-8.4 g/dL) and low albumin of 2.8 g/dL (normal range: 3.2-5.6 g/dL). Serum phosphorous was 4.5 mg/dL and magnesium was 1.3 mEq/L, both within normal limits.

The patient was started on the unit's standard refeeding protocol, which included progressive oral nutrition, beginning at 1400 kcal and increasing by 400 kcal every 2-3 days until a minimum of 1.4 kg/week of weight gain was achieved. Her care was under the guidance of a full multidisciplinary team comprised of an internist, registered dietician, psychologist, psychiatrist, and physical and occupational therapists. Vital signs and point of care fingerstick glucose levels were obtained in supine position every four hours on admission, with a subsequent reduction in frequency as medical stability was achieved. Due to the severity of her anemia, serum chemistries were obtained every other day during the first week of admission, as opposed to our standard unit protocol of daily lab monitoring, with titration of frequency thereafter based on medical stability. Blood draws for hematology counts were also minimized.

The hematology service was also consulted and recommended to provide five doses of ferric gluconate due to the low iron saturation of 17%, as well as folate supplementation at 2000 mg daily (serum folate not checked). They agreed with the presumed diagnosis of GMT, and a bone marrow biopsy was not performed given the high suspicion for GMT as well as the frailty of the patient. Her hemoglobin level showed gradual improvement during the hospitalization in congruence with the weight restoration (Figure 1).

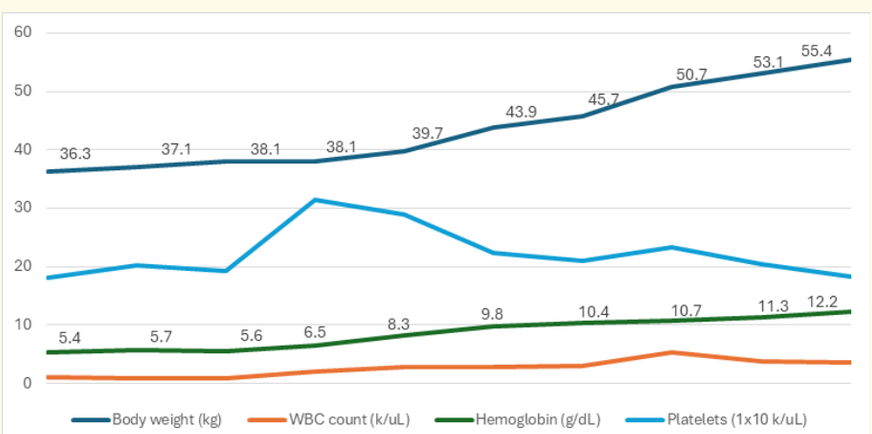

Figure 1: Complete blood counts and body weights.

At the time of discharge, hemoglobin had completely normalized (12.2 g/dL), although she still had leukopenia (3.5 k/uL). She had gained 19.1 kg over 51 days, achieving a BMI 20.7 kg/m^2, on a 4200-kcal meal plan at the time of discharge. Supplemental enteral nutrition was initiated two weeks into her admission due to increased gastrointestinal distress as the volume of her prescribed oral kcal intake increased, and this was continued for one month. An ED had also been fully ruled out, and her self-starvation was felt to be related to her cognition surrounding the tumor.

Discussion

A literature review of case reports published in English, describing GMT in individuals with diagnosed EDs or disordered eating habits, was completed in order to better understand GMT in this population. This yielded 31 case reports, including the individual discussed in this article (Table 1) [10-37]. Average age was 25 years, 81% of the individuals were females, and AN was the predominant diagnosis (84%)-two individuals were diagnosed with atypical AN [12,29], three patients were further classified into AN-R [16,28,32], and one was diagnosed with the binge/purge subtype of AN [14]. Additional cases of starvation included the following: avoidant restrictive food intake disorder (ARFID) [25], self-starvation of unspecified cause [18], exclusion of all starch from the diet [24], an unspecified eating disorder [21], and the individual described in the case report herein. Average percentage of ideal body weight (IBW) on initial testing was 58.9% (n = 13) with a BMI of 13.1 kg/m^2 (n = 24). Rates of weight loss preceding development of the GMT were provided for nine patients and ranged from 0.6 kg/month (over 6 months) to 7.83 kg/month (over 6 months). Vitamin B12 was normal in 15 cases and elevated in 1 case study; similarly, thyroid stimulating hormone was normal in all the cases (n = 6). Folate was low in one case but otherwise normal in the remainder of the cases (n = 14). Iron deficiency was present in four of eleven individuals, and copper deficiency was present in one of two individuals. MCV was normal in nine case reports (mean BMI of 11.97 kg/m^2) and high in six case reports (mean BMI of 17.4 kg/m^2). Three patients were treated with growth factors [10,13,34], three received blood transfusions [12,24,25], and one was treated with both blood transfusion and growth factors [28]; the rest were treated with nutritional support, without other interventions documented. Only 12 of the 31 case reports (39%) provided the amount of weight gained by the individual or a BMI at the time of the follow-up complete blood count or repeat bone marrow biopsy.

Twenty-two of twenty-eight individuals initially presented with leukopenia, and WBC counts had normalized in ten of those individuals after an average of 14 kg gained (weights provided for n = 7) while remaining low in five individuals who had gained an average of 14.8 kg (weights provided for n = 3); no follow-up WBC counts were provided in seven of these case reports. Range of time for normalization of leukopenia was 10 days [22] to years [19]. Twenty-five of twenty-nine individuals initially presented with anemia, and hemoglobin had normalized in nine of those individuals after an average 16.5 kg gained (n = 6) while remaining low in five individuals (only one case report documented a weight change, +10.4 kg); no follow-up hemoglobin counts were provided in 11 cases. Range of time for normalization of anemia was 24 days [15] to years [19]. Also, seventeen of twenty-five cases initially presented with thrombocytopenia, and ten of eleven of these cases had normal platelets at follow up-the individual in the case with continued thrombocytopenia at follow-up was also diagnosed with disseminated intravascular coagulation and ultimately passed away [15]; six of these cases did not document follow-up platelet values.

Five patients had repeat bone marrow biopsies. One individual had normalization of GMT on repeat bone marrow biopsy after gaining 10.4 kg over 10 days; leukopenia had also resolved although she remained anemic at day 10 [22]. Another individual showed normalization of GMT on repeat bone marrow biopsy at day 24 after unclear weight gain but had mild disseminated intravascular coagulation and ultimately passed away [15]. Case three described an individual who had normalization of GMT on repeat biopsy after BMI increased from 13 kg/m^2 to 16.5 kg/m^2 over six weeks, as well as normalization of leukopenia and thrombocytopenia, although she was still anemic [14]. Case four described an individual treated with growth factors who did not have complete resolution of GMT on repeat bone marrow biopsy after gaining an unknown amount of weight over 26 weeks; this last individual also still had leukopenia on follow up blood counts [13]. The final individual had a repeat biopsy after an unspecified amount of time without other relevant data provided [32].

Although the exact "nutritional hit" to the marrow in those with AN, as well as the amount of weight gain needed to normalize peripheral blood counts, remains unclear, resumption of caloric intake and weight gain do normalize the marrow irregularities and blood counts [39]. It seems that GMT can resolve fairly quickly with nutritional support--three of these individuals with repeat bone marrow biopsies showed resolution of GMT on repeat biopsy after a mean of 21 days and with modest weight gain of 10.4 kg [22] and a BMI increase of 13 kg/m^2 to 16.5 kg/m^2 [14]. However, these weight trends must be interpreted cautiously. Fluid/hydration status is over-looked in those with AN and so the effect of hemoconcentration on these peripheral blood counts is unclear, especially on initial testing before nutritional support is provided [38]. On the contrary, aggressive weight trends, such as the 27 kg gained over two months described by Hariz., *et al*. [29], suggests fluid retention.

Studies in rabbits suggest that hemopoiesis resumes at five weeks after resolution of an injury to the marrow [40], although the time course for resolution of the abnormal peripheral counts

remains unclear. It is possible that total body fat mass depletion, as opposed to lean tissue mass or total weight loss, better correlates with development of GMT in those with AN [6,41]; however, this has not been found in all studies [42]. The impact of weight suppression, or the delta change between one's current weight from their highest-ever weight, toward development of GMT and peripheral blood count abnormalities in AN, is also unclear. However, greater weight suppression seems to impact hemoglobin but not the other cell lines [43]. Furthermore, individuals with AN tend to consume low fat and low kcal diets with less decrease in their protein intake, but the impact of macro- and micronutrient deficiencies toward development of this condition remains unclear [44,45].

Given the poor correlation between the peripheral blood counts and the gross histologic changes of GMT seen on bone marrow biopsy or aspirate, the impact on the peripheral blood counts is more likely due to a marrow microenvironment that is unsuitable to hematopoiesis, believed to be caused by the increased deposition of the hyaluronic acid mucopolysaccharides associated with GMT [3]. It is within these bone marrow microenvironments, or "niches", that hematopoietic stem cells receive multiple regulatory signals, largely from mesenchymal stem cells residing nearby in the marrow, including numerous cytokines such as interleukin-6, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), and others [46]. Similarly, the function of mesenchymal stem cells are directly impacted by various immunomodulators such as adipokines and TNF [47,48]. Curiously, marasmus and kwashiorkor are rarely associated with GMT [49], unlike the increased incidence of GMT in those with AN. But, AN is associated with increased serum levels of TNF, compared to levels seen in primary malnutrition, such as marasmus and kwashiorkor [50]. Similarly, serum GM-CSF was found to be undetectable on admission and with weight gain in one group of adolescents with AN [51]. However, the contribution of malnutrition toward the immunomodulatory signaling within these niches, and how these niches change with refeeding, have not yet been directly elucidated.

Conclusion

GMT and reduced peripheral blood counts are frequently encountered hematologic complications in those with malnutrition and EDs. Although GMT seems to resolve relatively quickly on repeat bone marrow biopsy with nutritional rehabilitation and weight restoration, the direct impact of nutrition toward peripheral blood counts remains less clear, and the actual cause of the peripheral blood count irregularities in this population ultimately requires additional investigation.

Conflict of Interest

None.

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