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"Flowers" in the blood: A novel paired erythrocyte arrangement in a patient with chronic fatigue syndrome following infectious mononucleosis

Carrie E Burdzinski

ABSTRACT

Introduction: Chronic fatigue syndrome is a debilitating condition characterized by persistent fatigue, post-exertional malaise, myalgia, arthralgia, lymph node tenderness, impaired memory and concentration, autonomic irregularities, and other specific symptoms affecting multiple body systems. Diverse hypotheses have been investigated to ascertain the disease etiology. Some of these include metabolic and mitochondrial deficiencies, exposure to environmental toxins, dysautonomia associated with orthostatic intolerance, autoimmune reactions, neuroendocrine aberrations, and chronic viral infections. However, a consistently observed biomarker for chronic fatigue has not been identified. A comprehensive, standardized strategy for accurate diagnosis and successful treatment remains elusive.

Case Report: A 28-year-old Caucasian female presented with chronic fatigue persisting for nine months following infectious mononucleosis. Laboratory evaluation excluded classic causes of fatigue. Peripheral blood smear examination revealed numerous pairs of unusual nondiscocytic C-shaped erythrocytes, coupled in perpendicular crosses resembling four-petalled flowers. The presence of the erythrocyte pairs abated with the patient's recovery from chronic fatigue syndrome over a 24-month period. This erythrocyte arrangement has not been reported elsewhere in medical literature.

Conclusion: A novel erythrocyte "flower" formation was identified in a patient with chronic fatigue syndrome. The presence of this arrangement paralleled the course of the illness and was no longer observed upon recovery. The physiological relevance of the structure remains a subject for future research. Several hypotheses are suggested, including enhanced membrane deformability resulting from elevated catecholamine levels, and immune-mediated agglutination, possibly stemming from viral infection.

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Keywords: Chronic fatigue syndrome, Infectious mononucleosis, Erythrocytes, Hematology

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INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating condition characterized by persistent fatigue unresponsive to bed rest, postexertional malaise, myalgia, arthralgia, lymph node tenderness, impaired memory and concentration, autonomic irregularities, and other specific symptoms affecting multiple body systems [1]. Fatigue persisting for less than six months, or fatigue attributable to an identified organic cause such as hypothyroidism, preclude the diagnosis of CFS [2]. Based on clinical assessment, the worldwide prevalence of CFS is 0.76% [3].

Diverse hypotheses have been investigated to ascertain the disease etiology. Some of these include metabolic and mitochondrial deficiencies, exposure to environmental toxins, dysautonomia associated with orthostatic intolerance, autoimmune reactions, neuroendocrine aberrations in the hypothalamic-pituitary-adrenal (HPA) axis, and chronic viral infections [4–9]. The terms myalgic encephalomyelitis (ME), chronic fatigue immune dysfunction syndrome (CFIDS), and postviral fatigue syndrome (PVFS) are used to reflect the complex of abnormalities observed in CFS.

Despite several promising lines of investigation, a consistently observed biomarker for CFS has not been identified. A comprehensive, standardized strategy for accurate diagnosis and successful treatment remains elusive.

In this case report, I describe a patient with chronic fatigue syndrome subsequent to infectious mononucleosis. A novel erythrocyte arrangement was observed on peripheral blood smears examined periodically throughout the duration of the illness, lasting 24 months. The unusual erythrocyte pattern abated simultaneous with remission from CFS. To date, this erythrocyte finding has not been reported elsewhere in medical literature. It is suggested as being potentially associated with CFS.

The reader should be made aware that the patient presented in this case report is the author. Care has been taken to retain impartiality in the case presentation and analysis, and to minimize the potential for bias.

CASE REPORT

Physician workup: A 28-year-old Caucasian female presented with fatigue persisting for nine months following infectious mononucleosis (IM). She reported physical exhaustion, widespread muscle and tissue pain, tender lymph nodes, sleep disturbances, and sensitivity to light and sound. Physical examination confirmed orthostatic hypotension, slightly subnormal body temperature, and cold extremities replicable on each office visit. The patient was homozygous for methylenetetrahydrofolate reductase (MTHFR) C677T mutation. However, serum and erythrocyte folate levels were adequately maintained with vitamin supplementation. Co-existing diseases, health risk factors, and medication use were negative.

Blood was collected and evaluated using automated flow cytometry at regular intervals throughout the two-year duration of the illness in an attempt to determine the source of the persisting fatigue. Anemia and hypothyroidism, the two classic causes of fatigue, were excluded (Table 1). Borderline low erythrocyte count and hemoglobin concentration occasionally met the diagnostic criteria for mild anemia. However, the condition was transient and had no apparent correlation with fatigue severity. Although serum ferritin levels suggested tissue-level iron depletion, iron-deficiency anemia was not indicated as per normal hemoglobin concentration and mild macrocytosis. Other vitamin and mineral deficiencies associated with anemias, including vitamin B12, folate, and copper, were ruled out. Thyroid panel measures were borderline low but within the reference range precluding standard hormone therapy. Thyroglobulin and thyroid peroxidase antibodies were negative. All measures of the complete metabolic panel, including electrolytes, serum glucose, and liver function tests were within normal limits. The urinalysis was unremarkable. No organic cause of fatigue could be ascertained, and the diagnosis of chronic fatigue was assigned.

Table 1. Laboratory findings throughout a 24-month course of chronic fatigue syndrome.

	Patient results (mean of several samples)	Reference range
Red blood cells (RBC) (x10^6 RBC/μL)	3.79 ± 0.28	3.80-5.10
Hemoglobin (Hb) (g/dL)	12.0 ± 0.4	11.8-15.5
Mean corpuscular volume (MCV) (fL)	97 ± 2	80-98
RBC distribution width (RDW) (%)	14.2 ± 0.3	11.5-15.0
Serum ferritin (ng/mL)	7 ± 3	14-175
Total iron (μg/dL)	75	50-175
Iron binding capacity (mg/dL)	290	250-450
Serum vitamin B-12 (pg/mL)	1276	200-1100
Serum folate (ng/mL)	>24	>5.4
RBC folate (ng/mL)	719	>280
RBC copper (mg/L)	0.73	0.53-0.77
Thyroid-stimulating hormone (TSH) (mIU/L)	2.27 ± 0.5	0.40-4.50
Total thyroxine (T4) (mg/dL)	5.0 ± 0.3	4.5-12.0
Free triiodothyronine (fT3) (pg/mL)	2.3 ± 0.2	2.3-4.2
Reverse T3 (rT3) (ng/dL)	21	11-32

Blood film evaluation: The microscopic examination of blood has the potential to reveal cellular abnormalities that are not detectable via automated methods. Thus, I created peripheral blood smears from capillary blood extracted via the finger-prick method to screen for irregularities and infectious agents. Both

unstained and Wright's-stained slides were produced under standard conditions. Specimens were observed with light microscopy immediately after creation.

Erythrocyte color, size, and shape showed no apparent abnormalities, though occasional schistocytes were observed (frequency <5%). However, an unusual arrangement was regularly found in which pairs of nondiscocytic C-shaped erythrocytes appeared to be physically coupled in a perpendicular cross (Figure 1). Most frequently the structures were bisymmetric, though several off-centered, partially overlapping pairs were noted (Figures 2 and 3). I described these structures as erythrocyte "flowers", as the four lobes formed by the ends of the paired erythrocytes resembled classic four-petalled flowers. Frequency of the erythrocyte flowers was, on average, one per high-power field (x400). Their presence on both stained and unstained slides, and in the feathered edges as well as the near-body regions, suggested meaningful adherence between interacting cells rather than artifactual overlap.

Literature exploration yielded no documentation of this paired erythrocyte formation, nor was the arrangement recognized by several hematologists consulted informally. It was suggested that the coupling might represent cellular aggregation distinct from rouleaux or traditional agglutination.

Erythrocyte flowers continued to be identified on blood films collected and surveyed at periodic intervals throughout the duration of the patient's illness, persisting 15 more months. The patient recovered from the debilitating fatigue during this time without pharmacologic intervention. Orthostatic hypotension and temperature abnormalities persisted. However, the patient no longer complained of fatigue and no longer met the diagnostic criteria for chronic fatigue syndrome.

Concurrent with recovery from chronic fatigue, the paired erythrocyte flowers were no longer detected in several blood films examined at two-year follow-up.

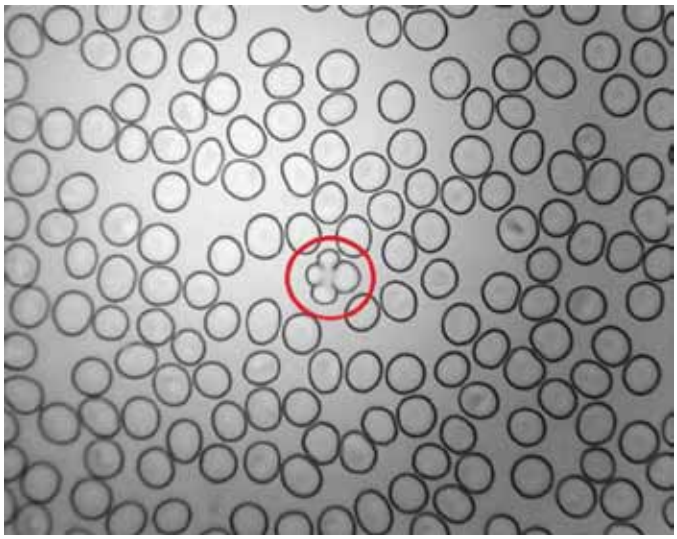

Figure 1: Typical appearance of an erythrocyte flower in a peripheral blood smear (Light microscopy, x400).

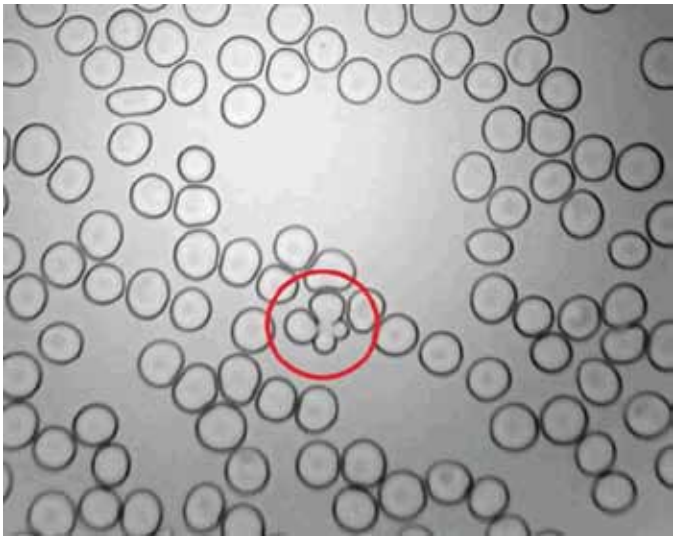

Figure 2: Off-centered erythrocyte flower in a peripheral blood smear (Light microscopy, x400).

Figure 3: Representative views of erythrocyte flowers (Light microscopy, x1000).

DISCUSSION

In this case report, I have presented a novel erythrocyte arrangement detected in a patient with chronic fatigue syndrome, the presence of which paralleled the course of the illness. This paired erythrocyte formation had not been reported in the medical literature at the time of observation.

Lubas et al. discovered and recently described this structure in canine blood, noting it as a curious incidental finding in 3.89% of routine veterinary blood smear examinations [10]. They have termed the arrangement "quatrefoil red blood cell," or "qRBC", after the cross on the flag of Pisa. The erythrocyte pairs were observed with greater frequency nearer the peripheral edges of the smears, consistent with the hypothesis of a larger aggregate structure. Follow-up study with electron microscopy supported the proposed morphology as a meaningful interaction between two erythrocytes. Statistically, significant correlation was found between specimens containing qRBCs and age of dog, decreased leukocyte count compared to controls, and anisocytosis [11].

If the paired erythrocyte arrangement is detected in controlled studies and confirmed as being associated with

chronic fatigue syndrome, several potential hypotheses may be considered for further investigation.

Unusual nondiscocytic erythrocytes, particularly those forming a "cupped" shape, have been previously associated with CFS [12]. Further, a direct correlation between catecholamine levels and erythrocyte membrane deformability has been demonstrated [13]. As patients with CFS frequently present with elevated resting catecholamine levels and exaggerated catecholamine response to upright tilt, it is possible that such patients have a greater likelihood of erythrocyte deformability [14, 15]. Erythrocyte doublet flowers may represent one possible outcome of enhanced membrane flexibility.

Cold agglutinin disease and immune-mediated "auto-agglutination" of erythrocytes are known sequelae of infectious mononucleosis [16]. The erythrocyte doublets described in this report may potentially represent another manifestation of agglutination in cases of CFS following viral infections.

Finally, the paired erythrocyte structure may offer an explanation for the transient mild anemia, mild macrocytosis, and mild anisocytosis occasionally noted on this patient's routine blood counts. In canines, agglutinated erythrocytes have been shown to yield errors in flow cytometry analysis: Mean corpuscular volume (MCV) is falsely elevated and red blood cells (RBC) count is falsely decreased [17]. It is possible that erythrocyte flowers or other aggregates may obscure accurate readings in standard blood analyses used to screen for traditional causes of fatigue.

CONCLUSION

A novel erythrocyte "flower" formation, consisting of two interlinked C-shaped erythrocytes, was identified in a patient with chronic fatigue syndrome. The presence of this arrangement paralleled the course of the illness, lasting 24 months, and was no longer observed upon recovery from chronic fatigue syndrome (CFS). The physiological relevance of the structure remains a subject for future research. If the arrangement is significantly associated with CFS, several hypotheses for its formation are suggested, including enhanced membrane deformability resulting from elevated catecholamine levels, and immune-mediated agglutination, possibly stemming from viral infection.

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Author Contributions

Carrie E Burdzinski – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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