Cyclic Neutropenia: A Case of Asymptomatic Appendicitis*

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ABSTRACT

A seven year old boy with a history of cyclic neutropenia (CN) was admitted to the hospital after developing fever and chills following a bicycle accident. After admission, he had a rapidly deteriorating hospital course leading to shock and death. At autopsy, acute appendicitis with resultant peritonitis and sepsis was diagnosed. The peculiar clinical and microscopic aspects of this case will be presented and contrasted with the more usual signs and symptoms of this cyclic disease.

Introduction

Cyclic neutropenia (CN) is a clinical syndrome of periodically occurring fever, aphthous stomatitis, malaise, chills, and often pharyngitis, lymphadenitis, and headache. Underlying the symptoms is a granulopoietic disorder that results in levels of blood polymorphonuclear leukocytes (PMNs) that cycle between normal levels and low to zero with a periodicity of approximately 21 days. The nadir lasts about three to five days. At this time, the marrow shows a number of granulocyte precursors that develop as far as the metamyelocyte stage, but no further. Interestingly, many of the precursors have been reported to be abnormal and contain autophagic vacuoles. The marrow of CN patients in the neutropenic phase has been said to contain nuclear dust from destroyed PMN precursors.27 Although these two observations have been disputed, other ultrastructural abnormalities have been seen elsewhere.26

Following the neutropenia, these precursors develop as a wave during which time the symptoms clear. The unique characteristic of cyclic neutropenia (CN) is its periodicity, allowing regular blood counts to differentiate effectively this disease from aplastic anemia or drug-induced granulocytopenia. No genetic link has been established, although several familial cases have been reported.7,33 The disease is generally one of morbidity, not mortality. Deaths have been reported, however, owing to infectious causes.1,4,33 Although there are two types, adult-onset and child-onset, only the latter will be discussed here.

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Case History and Pathologic Findings

This case is one of an eight year old white male who had a history of CN, with polymorphonuclear (PMN) levels dipping to zero at the nadir of his cycles. He presented in the emergency room after suffering a cardiopulmonary arrest at home approximately 48 hours after a bicycle accident. He had complained of fever and shaking chills the night prior to arrival. The symptoms were of sudden onset, with no prodrome.

At autopsy, the patient was diagnosed as having had appendicitis that ruptured, leading to peritonitis and septic shock with subsequent cardiopulmonary arrest. The microscopic findings consisted of an intense inflammatory reaction in the appendix comprising numerous lymphocytes and sporadic macrophages and plasma cells with a fibrous exudate over the serosa (figure 1). Areas of necrosis were apparent, and Gram staining revealed Gram (+) cocci and Gram (−) rods. No PMNs were present, a finding that is consistent with his complete blood count (table I).

The patient had a "mushy spleen". There was attenuation of the white pulp with congestion of the red pulp. There was a large number of plasma cells (figure 2). The marrow showed reduced myelopoiesis, (M:E) ratio of approximately 1:1. There was a slight

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Figure 1. Serosal involvement of the appendicitis. There is complete absence of neutrophils. The inflammatory cells are lymphocytes and plasma cells. (100×).

Figure 2. Spleen with extensive plasma cell infiltrate (400×).
reduction in the number of megakaryocytes. There were a fair number of promyelocytes and metamyelocytes, as well as a few band forms. Mature neutrophils were not present (figure 3). An occasional eosinophil was noted.

An additional diagnosis was made of a large hematoma of the inner thigh.

Discussion

The patient was highly predisposed to severe complications to a common enough childhood mishap. The absence of marrow PMN reserves left the patient susceptible to infection. The appearance of the appendix, completely devoid of PMNs, underscores the patient’s lack of first line inflammatory defense. The serosal involvement indicated a peritonitis in the region of the appendix and cecum. The raised number of leukocytes suggested that an inflammatory response was mounted. It is noteworthy that 97 percent of them were lymphocytes, indicating an absolute lymphocytosis. This attempt was ineffective and sepsis followed, suggested anatomically by the “mushy spleen” containing many plasma cells and an attenuated white pulp. The patient’s hematoma followed from his accident. The extent of the bruising, however, was probably aggravated by the patient’s thrombocytopenia (20,000 per μl). The low platelet count could have been either a part of the patient’s cyclic neutropenia or a result of disseminated intravascular coagulation subsequent to a long term infection.

A similar set of symptoms was seen in a CN patient who died from Clostridium sphenoides gastroenteritis. This patient had abdominal cramps, fever of 39.3°C, which faded with time. The whole course from onset to death was 29 hours, approximately the same as for our patient. A second patient was reported to have superficial ulcerations of the colon (as viewed via a colostomy) that came and went with his neutropenic episodes. Such ulcerations could provide

**FIGURE 3.** Hypocellular bone marrow showing reduced M:E ratio and lack of mature granulocytes (400×).
Foeholds on the road to peritonitis for ordinarily non-invasive organisms such as the C. sphenoides seen in one fatal case. ¹⁴  

The most curious aspect of our case is the lack of symptoms. As mentioned, fever, chills, malaise, etc. are usual symptoms found in the neutropenic phase of CN. Not only were there no symptoms for the appendicitis, there were none for the underlying disease either. By its oddity, this case may shed light upon the pathophysiology of pain, fever, and on the relationship between granulopoiesis and the other blood lines.  

Cyclic neutropenia has been studied extensively in relationship to production of other blood cell types. Generally, CN is believed to be a stem cell problem that leaves granulocytes arrested at the metamyelocyte stage in the bone marrow. It is not a problem of peripheral sequestration or of shortened cell half life as shown by animal models. ⁸ ⁹ Additionally, monocytes and lymphocytes have been observed to cycle in a pattern up to 180° off from the neutrophil periodicity. ⁵, ¹³ In fact, frank monocytosis has been noted in several patients. ²⁵ Furthermore, a rise in B and pre-B lymphocytes has been associated with the production of a hormonal factor found in the urine of cyclic neutropenics that stimulates the proliferation of pre-B cells. ²¹ In grey collie dogs (the animal models for CN), the proportion of B cells is increased, and the percentage of the subtypes of T lymphocytes is altered. ³⁰ Whether or not the rises and/or alterations in these other leucocyte lines are compensatory to the lack of first line defense or an inherent part of the disease remains unclear.  

There have been a number of hypotheses posed to explain the etiology of cyclic neutropenia. These include both positive ²⁵, ³² and negative ¹² feedback by mature and/or dying neutrophils on developing granulocyte precursors. Lymphocytes, too, have been proposed to play an inhibitory role on granulocytopoiesis in CN. ¹⁹  

One intriguing possible etiology of CN is that the problem may be with the monocytes and not the neutrophils. One study suggested that interruption of the cycling of the neutrophils did not halt the cycling of the monocytes. ²⁹ In an in vitro study, monocytes were found to produce a granulocyte colony forming agent that could raise PMN levels. ⁶ Further evidence would be required to support this theory, but there is enough evidence at present to suggest that although CN is billed as a neutrophil disorder, it is more likely a disorder of multiple blood cell lines.  

As mentioned, fever is a normal component of the clinical picture of CN. This fact contrasts with the classical thinking that PMNs are the producers of an endogenous pyrogen (EP) that is stimulated by Gram (+) bacteria, endotoxins, and various other stimuli. ² Recent experiments have demonstrated that the results of the classic experiments were due to contamination of the PMN culture by monocytes and macrophages. ¹¹, ¹⁸ Monocytes were subsequently shown to produce EP at levels 10 to 30 times higher than PMNs. ³, ¹⁸  

The EP has been demonstrated to be Interleukin-1, which has been hypothesized to act via a central mediator suggested to be prostaglandin E1. ¹⁰ These findings support the observations that CN patients have fever even with the complete absence of neutrophils but in the presence of relative or absolute monocytosis. Why our patient was afebrile might be explained by reviewing his complete blood count (CBC) and noting that monocytes comprised only two percent of his total white cells (table I). Why he had a lack of monocytes is unclear and contrasts with the normal cyclic neutropenia picture. It is possible that what
monocytes there had been were quickly overwhelmed by the infection. This final burst of monocytic activity may have perhaps resulted in the fever that eventually developed immediately prior to the patient's demise.

The second enigma of our case is the lack of pain accompanying the patient's appendicitis. Several mediators such as prostaglandin E2 and leukotriene B4 play a role in local pain transduction. Both are produced by leukocytes. The LTB4, C5a, and other mediators depend on PMNs in their role as hyperalgesics. Without PMNs to produce this key mediator, one would expect little pain to be produced under conditions that would otherwise elicit this reaction. That our patient was without pain, even when on the verge of appendiceal rupture is consistent with the limited physiological response of which the cyclic neutropenic is capable.

With such a limited understanding of the pathophysiology of CN, no obvious treatment comes to mind. Splenectomy has been tried, although CN is not a problem of splenic sequestration. Lithium carbonate has been used effectively in the grey collie dog, however, its efficacy has been uneven in human patients. Prednisilone and prednisone, too, have been explored. No one treatment has had more than sporadic success. Supportive and prophylactic antibiotic therapy remains the mainstay of CN therapy. As in our case, complications to CN can break the "rules" governing clinical symptomatology. The clinician, therefore, must be very aware of the condition of the patient having this interesting and complex disease.

References

18. HANSON, D. F., MURPHY, P. A., and WINDLE, B. E.: Failure of rabbit neutrophils to secrete endogenous pyrogen when stimulated with


