Cyclic Neutropenia with Giant Follicular Lymphoblastoma and Lymphosarcoma

Report of a Case with Splenectomy

By ROBERT P. NATelson, CAPT., MC, USA

CYCLIC OR PERIODIC NEUTROPENIA is a rare disorder characterized by the rhythmic recurrences, approximately every fourteen to twenty-one days, of leukopenia with neutropenia, fever, and buccal ulcerations. In 1949, Reimann and deBerardinis reviewed fourteen previously recorded cases and described two additional cases that had come to their attention by personal communications. Since this paper, there have been three additional reports of this entity and a fourth report which is a complete record of one of the patients Reimann and deBerardinis had included in their review. The etiology of this disorder is obscure. There have been many proposed theories on the etiology, including the infectious, endocrine, and allergic, all lacking confirmation.

Four cases have had coexistent disorders: three of them showed diabetes insipidus, hemolytic icterus, and bronchial asthma; in the fourth there was a postmortem finding of lymphosarcomatosis. Specific treatment has varied, including pentnucleotide, small pox vaccinations, pyridoxine, antihistaminics, yellow bone marrow, liver extracts, and x-ray therapy, all of which did not modify the course of the disorder. Splenectomy has been the most effective measure. It has been performed in eight cases of cyclic neutropenia with recorded benefit in all but two. Pituitary adrenocorticotropic hormone (ACTH) was administered to the last reported case with “favorable changes in the blood and bone marrow.”

The following report is a case characteristic of the entity cyclic neutropenia. In addition to the presence of this rare disorder, there was the unexpected discovery of a coexistent lymphosarcoma. The histologic characteristics of the lymphosarcoma suggested its origin as a giant follicular lymphoblastoma. This is the second reported case of lymphoma with associated cyclic neutropenia. The case of cyclic neutropenia in which lymphoblastoma was unexpectedly discovered at postmortem examination is the only record of the combination of cyclic neutropenia with lymphoma found in the literature. The effect of cortisone administration during a neutropenia-free stage and the effect of ACTH on the leukocyte values during a neutropenic stage were studied. The hematologic and clinical effect of splenectomy will also be described.

Case Report

This 26 year old white female of Hungarian descent, when first seen in July, 1952, related she had the onset of recurrent sore throat, buccal ulcers, and fever in 1947. This triad of symptoms persisted with periodic exacerbations until July, 1952. At this time, she developed a posterior cervical adenopathy and profuse gingival bleeding. From the Medical Service, William Beaumont Army Hospital, Fort Bliss, Tex. Submitted March 3, 1953; accepted for publication April 6, 1953.

The author wishes to acknowledge his indebtedness to Captain Carolyn M. Anthony, M.S.C. and Mrs. Vivian Falzett for their technical assistance; to Colonel Maurice C. Davidson, Lieutenant Harvey S. Rosenberg, Captain Edwin T. Nishimura, and Lieutenant Ronald O. Germain for their advice and cooperation.
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symptoms recurred about every two to three months. A white blood cell count was first performed in 1948, when it was found to be low. These acute episodes occurred with greater frequency and severity after 1949, occurring usually every two to four weeks, with an average interval of three weeks. A typical episode was characterized by a feeling of fatigue, malaise, and irritability for one to two days, followed by the appearance of high fever, large throat ulcers, severe soreness of the throat, frequent nausea and vomiting, generalized, severe, colicky abdominal pain, and occasional diarrhea. The acute episode lasted about three to five days, followed by a period of gradual improvement over a similar period.

The past medical and family histories were not significant.

On physical examination, she was a well developed, very thin, white female who appeared chronically ill. The oral temperature was 102 F., pulse 90, and blood pressure 100/80. Several large, deep, clean, punched-out ulcers measuring about 2 to 5 mm. in diameter were present in the tonsilar area and on the posterior pharyngeal wall. There was no significant inflammation about the ulcer. Small, discrete, tender, anterior cervical nodes were present. There was no other significant lymphadenopathy. On abdominal examination, there was diffuse upper abdominal tenderness without spasm or rebound. The liver and spleen were not palpated. The remainder of the physical examination was entirely within normal limits.

Laboratory examination on admission revealed the white blood cell count to be 2850 per cu.mm., with 8 per cent neutrophils and 92 per cent lymphocytes. The red blood cell count was 3,400,000 per cu.mm., with 45 per cent neutrophils and 55 per cent lymphocytes. The hemoglobin, 11.1 Gm. The stained smear demonstrated an abundance of platelets. The routine urinalysis was within normal limits. The blood serology by the cardiolipin micro techinic was negative. Subsequent red blood cell counts and hemoglobin determinations were either within normal limits or demonstrated a mild hypochromic normocytic anemia. Bone marrow studies during the subsiding phase of the neutropenia have shown granulocytic hyperplasia with an increase in the immature forms, particularly of the promyelocytes. During the neutropenia-free periods, marrows have been entirely within normal limits. Smear and culture of the buccal lesions for pathogens and fungi showed rare gram positive diploccci on smear and alpha hemolytic streptococci predominating on culture. Numerous additional laboratory examinations including liver function tests, blood agglutinations, and blood cultures showed no abnormality.

The chest x-ray was negative. An upper gastrointestinal series suggested the presence of moderate hypertrophic gastritis. On re-examination four months later, this finding was no longer present. Other x-ray studies performed, including a barium enema, skeletal survey for metastases, and repeat chest films, were negative.

Numerous serial leukocyte counts and differential counts revealed the rhythmic depression of both the total number of leukocytes and the neutrophils one to two days before the onset of her acute symptoms. (See table 1 for the leukocyte values for a three week period demonstrating two typical cycles eighteen days apart and figure 1 for a graphic record of the cyclic depression of the neutrophils during three month periods in 1949 and 1952.) Clinical improvement paralleled a rise in the white blood cell values. With the leukopenia and neutropenia there typically occurred an absolute monocytosis. The monocye count commonly rose to about 50 per cent during a leukopenic phase.

Hospital records since 1950 were reviewed and revealed neutropenic episodes occurring approximately every fourteen to twenty-one days.

The effects which are produced by ACTH and cortisone on the total leukocyte count, the differential count, and the absolute eosinophil count are listed in table 1. On August 10, 1952, at the onset of a neutropenic phase (WBC, 3050 per cu.mm. with 22 per cent neutrophils), 25 mg. of ACTH was given intramuscularly. There was no change in the absolute eosinophil count of 132 per cu.mm. of blood in four hours. On the following day (WBC 3200 per cu.mm. with 34 per cent neutrophils) the oral administration of 100 mg. of cortisone also had no appreciable effect on the absolute eosinophil count. On August 26, 1952, during a period of remission, (WBC 4500 per cu.mm. with 41 per cent neutrophils) the patient was again given ACTH, 25 mg. intramuscularly. There was a significant drop in the eosinophils from 110 per cu.mm. to 44 per cu.mm. During the subsequent leukopenic episode (WBC 2850 per cu.mm. with 4 per cent neutrophils) the absolute eosinophil count was 22 per cu.mm. which suggests an "adequate" adrenal cortex response to the stress of the leuko-
penic episode. On August 29, 1952, during a neutropenic phase, (WBC 3100 per cu.mm. with 3 per cent neutrophils) the patient was given an eight hour intravenous infusion of 20 mg. of ACTH. Hourly white blood cell counts and differential counts for four hours and counts eight and twelve hours after the start of the ACTH were performed. A satisfactory response in the absolute eosinophil count was demonstrated by a reduction from a base level of 220 per cu.mm. to 22 per cu.mm. four hours after, and zero eight hours after the start of the ACTH. During this period there was also noted a maximum drop in leukocytes from 3100 to 1700 per cu.mm. There was no significant change in the very low neutrophil values. On September 8, during a neutropenia-free stage, (WBC 5600 per cu.mm. with 54 per cent neutrophils) cortisone tablets, 25 mg. orally four times daily, were administered to determine if this hormone would prevent or ameliorate a neutropenic episode. Four days later the patient had the onset of one of her most severe episodes of sore throat, buccal ulcers, and toxemia. The absolute eosinophil count had dropped from a base level of 176 per cu.mm. to 66 per cu.mm., and the leukocyte count had dropped to 3350 per cu.mm. with 6 per cent neutrophils. The cortisone was discontinued after four days of administration when the patient manifested such severe symptoms. It is noteworthy that the recurrence was fourteen days from the last cycle; therefore, apparently, the cortisone neither precipitated nor prevented the rhythmic return of neutropenia.

Other studies to elucidate the etiology of cyclic neutropenia were performed. A Rowe elimination diet to discover a possible food allergy failed to alter the course of this disorder. One cc. of histamine diphosphate was administered subcutaneously during a neutropenic-free interval in a fruitless effort to provoke an episode. During an episode of neutropenia, Benadryl was administered intravenously—30 mg. the first day, 60 mg. the second—without any significant effect. Administration of frequent small blood transfusions were without specific effect upon the leukocyte values, but, they were noteworthy for the decrease in toxicity and speedier clinical recovery from an episode which they produced.

During her many episodes of neutropenia with infection, she received varied antibiotics.
ROBERT P. NATELSON

She responded most promptly to the broad spectrum antibiotics, Aureomycin, Chloromycetin and Terramycin. Penicillin and streptomycin were less effective.

On October 16, 1952, a splenectomy was performed by Colonel Norman W. Anderson. The spleen was approximately twice the normal size and weighed 295 Gm. The liver appeared normal in external appearance, but it was moderately enlarged. It extended two finger breadths below the right costal margin and occupied the epigastrium and extended into the left upper quadrant. On exploration of the abdominal cavity, several calcified mesenteric nodes were palpated, one of which was removed for microscopic examination.

It revealed a thoroughly calcified structure without evidence of its etiology. There were also numerous soft nodes in the entire mesentery and in the retroperitoneal area. These varied in size from 1 to 3 cm. in diameter. A biopsy of one of these nodes revealed lymphosarcoma. Dr. Henry Rappaport, of the Armed Forces Institute of Pathology, reviewed the sections and judged that the lymphosarcoma had its origin in a malignant lymphoma of the follicular type. Sections of the spleen, as reviewed by Dr. Rappaport, revealed "many of the Malpighian corpuscles considerably enlarged and varying in shape. In most of them, reaction centers are lacking. They are composed of small lymphocyte cells very similar to those seen in the lymph node sections. The histologic picture strongly suggests involvement of the spleen by the lymphomatous process. The sections of liver show lymphocytic infiltrations of the portal fields which are, in themselves, not diagnostic of lymphoma, but in the presence of lymphoma elsewhere, may represent early involvement of the liver." 

**Table 2.—Leukocyte Values Before and After Splenectomy**

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* Two hours after splenectomy.

It revealed a thoroughly calcified structure without evidence of its etiology. There were also numerous soft nodes in the entire mesentery and in the retroperitoneal area. These varied in size from 1 to 3 cm. in diameter. A biopsy of one of these nodes revealed lymphosarcoma. Dr. Henry Rappaport, of the Armed Forces Institute of Pathology, reviewed the sections and judged that the lymphosarcoma had its origin in a malignant lymphoma of the follicular type. Sections of the spleen, as reviewed by Dr. Rappaport, revealed "many of the Malpighian corpuscles considerably enlarged and varying in shape. In most of them, reaction centers are lacking. They are composed of small lymphocyte cells very similar to those seen in the lymph node sections. The histologic picture strongly suggests involvement of the spleen by the lymphomatous process. The sections of liver show lymphocytic infiltrations of the portal fields which are, in themselves, not diagnostic of lymphoma, but in the presence of lymphoma elsewhere, may represent early involvement of the liver."
Two hours after the splenectomy, the white blood cell count had increased from the immediate presurgical value of 3250 per cu.mm. with 46 per cent neutrophils to 17100 per cu.mm. with 76 per cent neutrophils. (See table 2 for the leukocyte values shortly before and after splenectomy and figure 2 for a graphic representation of the cyclic neutropenia before and after splenectomy.) On October 21, twelve days after the onset of the previous episode of neutropenia and five days after the splenectomy, leukopenia with neutropenia recurred. The neutrophils almost completely disappeared during this episode (on October 23, there were only 49 neutrophils per cu.mm. of blood), but the total white blood cell count remained on an average above 4000 per cu.mm. This episode clinically was not so severe as those prior to splenectomy. The ulcers were not as marked and the toxemia was not as severe. It should be noted, however, that the patient was on antibiotics at the onset of this episode which most probably influenced its intensity. On November 24, fever, sore throat, buccal ulcers, and abdominal pain recurred, but the total white blood cell count and neutrophil count were only moderately depressed (WBC 5600 per cu.mm. with 41 per cent neutrophils). The symptoms were milder and of shorter duration than previous episodes. On December 9, 1952, fifteen days later, there again occurred a similar episode of less severity than those prior to splenectomy (WBC 3700 per cu.mm. with 30 per cent neutrophils).

The patient has been seen at frequent intervals in the past four months since the splenectomy, and there have been rhythmic recurrences every two to four weeks of mild buccal ulcers, low grade fever, and moderate depression of the leukocyte values, but the abdominal pains have not been significantly ameliorated. The total leukocyte counts and neutrophil values, excepting the first neutropenic episode after splenectomy, did not drop below 3000 white blood cells per cu.mm. or 28 per cent neutrophils. (See figure 2 for a graphic comparison of four cycles before and four cycles after splenectomy.)

With the revelation that the patient had a lymphoma, it was thought that the severe, recurrent abdominal pain could be due to retroperitoneal or abdominal lymph node involvement or both. Accordingly, x-ray therapy, 200 r on alternate days to both the abdominal
and retroperitoneal areas by anterior and posterior ports, was started on November 24, 1952 by Colonel Douglas S. Kellogg, and temporarily discontinued on December 9, 1952, (after a total of 1200 r) at the onset of another relatively "mild" episode of leukopenia and neutropenia. The x-ray therapy decreased the abdominal pain only little; however, the patient did feel considerably stronger, began to gain weight, and looked considerably improved.

**Discussion**

There has been no adequate definition of the etiology of cyclic neutropenia. Medical forms of therapy have been uniformly unsuccessful. Splenectomy has been the only sustained therapeutic measure, although it has not been completely curative or of benefit in all cases.

The hematologic response to ACTH and cortisone was studied with the purpose of elucidating any etiologic relationship of the pituitary-adrenal axis to this disorder. Cortisone was administered to determine its possible therapeutic value.

It is of interest that the administration of ACTH during a neutropenic phase caused a further depression of the leukocyte count and no significant change in the already very low neutrophil count. This finding parallels the experience of Reimann and deBerardinis, who observed a decrease in both the leukocytes and neutrophils with ACTH administration in their patient with cyclic neutropenia, and is contrasted with the increase in both the total white blood cell count and neutrophils with ACTH administration in the normal individual.

That cortisone did not prevent the development of a neutropenic episode suggests, but certainly does not prove, that the cyclic neutropenia does not result from a hypersensitivity or "allergic" phenomenon upon myelopoiesis. The cortisone was not continued throughout a complete cycle, for the particular cycle which occurred during cortisone therapy appeared to be unusually severe, and it was thought, since the neutropenia was not prevented, that further administration of cortisone would have no specific effect and might be deleterious. No definite conclusions can be made from this experience with cortisone, but the evidence suggests that its efficacy in cyclic neutropenia is slight. In the previously reported case of cyclic neutropenia in which ACTH was administered prior to splenectomy, there was a dramatic clinical improvement coupled with favorable changes in the blood and bone marrow. There is, however, no clear evidence that the improvement was not due to a combination of the antipyretic and antitoxic effects of the ACTH coincident with an expected cyclic remission of neutropenia, rather than to a specific effect of the pituitary hormone.

Splenectomy in the present case appeared to be of benefit. Although the cyclic episodes of neutropenia continued, they were less severe and were clinically manifested by considerably less toxemia and fever, and less severe buccal ulcerations. Hematologically, the total leukocyte values remained at near normal levels, but the neutrophils did have moderate depressions at rhythmic intervals (except the single episode of profound neutropenia seven days after splenectomy). It must be noted, however, that the patient was on antibiotics for two weeks after splenectomy, and nine and one-half weeks after splenectomy, x-ray therapy for the lymphoma was initiated. These factors may have modified the course of her disease. The two month period between the time the antibiotics were dis-
continued following splenectomy and the start of x-ray therapy was, however, remarkable for the mildness of the episodes and the lack of severe neutropenia which suggests that splenectomy was of value. Unfortunately a longer follow-up period after splenectomy was not possible, so that a definite statement regarding its long range value cannot be made.

Although the occurrence of a lymphoma with cyclic neutropenia may be a fortuitous one, it is most likely a related occurrence. This is particularly so, because of the previously reported case of diffuse lymphosarcoma discovered at autopsy in a patient with cyclic neutropenia. Cyclic neutropenia is of rare enough incidence to make the presence of two cases of lymphosarcoma probably more than a coincidental occurrence. With the strong suggestion that the present case had an underlying giant follicular lymphoblastoma, it is conceivable that cyclic neutropenia may be a rare manifestation of this type of lymphoma. Since giant follicular lymphoblastoma has a more chronic and comparatively milder course than lymphosarcoma, it would seem that the cyclic neutropenia has been associated with the former disorder and that the lymphosarcoma is an end development of the giant follicular lymphoblastoma. The occurrence of lymphosarcoma with giant follicular lymphoblastoma is not unexpected, for the idea has been advanced by Baehr, Klemperer, and Rosenthal, and Meyer that giant follicular lymphoblastoma is actually a form of lymphosarcoma.

The occurrence of cyclic neutropenia with giant follicular lymphoblastoma-lymphosarcoma does not, of course, elucidate the etiology of cyclic neutropenia. The lymphoma, however, may be a pathway to a common denominator which is an important factor in the development of all cases of cyclic neutropenia, regardless of etiology. This common denominator may be a specific alteration of the reticuloendothelial system. Lymphomata are basically neoplasia of cells of reticuloendothelial origin. It is known that leukopenia may occur in the lymphomata-giant follicular lymphoblastoma, lymphosarcoma, and Hodgkin’s disease. Secondary hypersplenism with depression of one or more of the blood elements has been observed in giant follicular lymphoblastoma and in Hodgkin’s disease. The leukopenia in such disorders may occur in the absence of widespread marrow involvement.

The pathogenesis of cyclic neutropenia in giant follicular lymphoblastoma is obscure but may be related to hypersplenism. Splenectomy with removal of a large unit of hematopoietically active reticuloendothelial tissue has been responsible for improvement with amelioration of symptoms and a rise of leukocytes and neutrophils in cyclic neutropenia, as it has in idiopathic chronic neutropenia. Splenectomy, however, was performed in a reported case of giant follicular lymphoblastoma with hypersplenism manifested by thrombocytopenia and neutropenia. The thrombocytopenia was corrected, but paradoxically the neutropenia persisted. Splenectomy may be efficacious, as it appeared to be in the present case, by the removal of “hypersplenic factors”. The concept of the spleen exerting a normal inhibitory effect upon myelopoiesis which may be increased in the presence of splenomegaly has been emphasized by Dameshek. The hypersequestration theory with increased selective destruction of blood elements by the spleen, as presented by Wiseman and Doan, may also be a factor. The involvement of the spleen by the lymphomatous disorder may have
enhanced the myelopoietic inhibition or hypersequestration effects of the spleen. Excessive concentrations of lysolecithin or some similar lytic enzyme or enzymes in the spleen, in addition to reticuloendothelial cell hyperplasia and hyperphagocytosis, have also been suggested as mechanisms in the development of the hypersplenic syndrome. The exact mechanisms of hypersplenism are still obscure and may well be a combination of these theories plus unknown factors.

After the suggestion that hypersplenism plays a role in the pathogenesis of cyclic neutropenia, the factors against such a theory should be considered. The main criterion for the presence of the entity, hypersplenism, and for the indication for splenectomy as stressed by Wiseman and Doan is the presence of a marrow hyperplasia of those cells which manifest a peripheral depression. Although a shift to the left with an increase in promyelocytes has been noted in the present case, the marrows were taken after the maximum depression of blood neutrophils. During the neutropenia-free periods, the marrows were entirely within normal limits. Unfortunately, serial marrows were not obtained before and during the early part of an acute episode. Fullerton and Duguid have made serial bone marrow studies in their case of cyclic neutropenia. They performed eight marrow aspirations at intervals of three to six days during one typical cycle and demonstrated a decrease in the early forms of the myeloid series a few days before the fall of neutrophils in the blood. There then occurred a progressive increase in the marrow myeloblasts, then neutrophilic promyelocytes and neutrophilic myelocytes shortly before the increase in peripheral neutrophils. Their serial marrow studies demonstrated, therefore, that there was an actual depression in the neutrophil precursors which was responsible for the peripheral neutropenia. If the present case actually had a rhythmic hypoplasia of the neutrophilic precursors, a beneficial result from splenectomy paralleling the response of classical cases of hypersplenism would not be expected. In view of the incomplete hematologic response to splenectomy evidenced by this case, such a situation may have existed. Although the total leukocyte values did rise after splenectomy, the absolute neutrophil count dropped to a very low level during her first cycle after splenectomy and, subsequently, has been moderately depressed at cyclic intervals.

Benefit from splenectomy may have resulted from the removal of the spleen’s normal inhibitory effect upon the bone marrow. In hypoplastic anemia, a beneficial hematologic and clinical effect with splenectomy has been observed occasionally by Welch and Dameshek. It was their belief that improvement was secondary to the removal of the spleen’s normal inhibitory effect upon the bone marrow. A parallel situation may exist in the present case.

**SUMMARY**

1. A case of the rare disorder cyclic neutropenia with giant follicular lymphoblastoma and lymphosarcoma is reported.

2. Adrenocorticotropic hormone administration during a neutropenic phase resulted in a further depression of the total leukocyte count and no significant change in the already very low neutrophil count. Cortisone did not prevent or ameliorate a recurrence of neutropenia.

3. Splenectomy resulted in less depression of the total leukocyte and neutro-
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phil values and a considerable amelioration of the symptoms during the continued cycles; however, because of the short follow-up, a definite statement on the long range value of splenectomy cannot be made.

4. The pathogenesis of cyclic neutropenia is discussed with particular reference to its relationship to lymphoma and hypersplenism.

REFERENCES

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Cyclic Neutropenia with Giant Follicular Lymphoblastoma and Lymphosarcoma: Report of a Case with Splenectomy

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