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Severe Neutropenia in Infectious Mononucleosis

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Mild neutropenia is a well-known concomitant of infectious mononucleosis caused by the Epstein-Barr virus (EBV) occurring in the first weeks of illness. However, severe neutropenia (less than 200 polymorphonuclear leukocytes per μl) is not generally regarded as a complication of infectious mononucleosis. Three patients were seen with severe neutropenia and EBV infection, and an additional eight cases were found in the literature. In two of the latter cases the neutropenia was fatal.

In the 11 cases the severe neutropenia began 14 to 40 days after illness and usually lasted for three to seven days. At the time of severe neutropenia, studies of marrow specimens showed increased proportions of promyelocytes and myelocytes. Our data suggest that EBV infection is the proximate cause of the severe neutropenia in some patients with infectious mononucleosis and that in such cases close observation and early treatment of suspected superinfections is necessary.

INFECTIOUS MONONUCLEOSIS is a common, self-limited illness characterized by fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis and a positive heterophil agglutinin test.[1-4] Rises in specific antibody titers to the causative agent, the Epstein-Barr virus (EBV) have recently been used to confirm questionable cases.[5,6]

Mild granulocytopenia (1,000 to 1,800 polymorphonuclear cells per μl) early in the course of infectious mononucleosis is well recognized,[7] occurring in as many as 40 percent of cases. The detailed studies by Carter[8] and Cantow and Kostinas[9] documented a reproducible fall in total circulating granulocyte counts during the first and second weeks of illness as the atypical lymphocyte counts were rising. Although severe neutropenia (less than 200 per μl) has been seen in several patients with infectious mononucleosis, this complication is not widely recognized.[1,2,10]

We recently saw three patients with infectious mononucleosis and severe neutropenia. We present the clinical and laboratory findings together with a review of those cases in the literature for which there was complete hematologic and serologic documentation of both infectious mononucleosis and severe neutropenia. These cases show a reproducible pattern of clinical and laboratory

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ABBREVIATIONS USED IN TEXT

anti-EBNA = anti-Epstein-Barr nuclear antigen
anti-VCA = antiviral capsid antigen
CMV = cytomegalovirus
EBV = Epstein-Barr virus
SGOT = serum glutamic oxaloacetic transaminase

observations strongly suggesting EBV as the agent causing severe neutropenia.

Reports of Cases

CASE 1. A 16-year-old girl was first seen on December 1, 1976, for fever, sore throat and malaise. She was taking meprobamate, 400 mg per day, for dysmenorrhea. She was treated with erythromycin for one week but fever, pharyngitis and cervical adenopathy continued, and hepatosplenomegaly subsequently developed. At that time laboratory data included the following values: hematocrit, 36 percent; leukocyte count, 7,400 per cu mm, with 1,700 polymorphonuclear cells per cu mm, 1,850 mature lymphocytes per cu mm, 3,700 atypical lymphocytes per cu mm and 150 monocytes per cu mm; normal platelets; erythrocyte sedimentation rate, 26 mm per hour; bilirubin, 0.7 mg per dl; alkaline phosphatase, 330 IU per liter; lactic dehydrogenase, 405 units per ml; serum glutamic oxaloacetic transaminase (SGOT), 235 units per ml, and a positive heterophil test.

An examination on December 22 showed no hepatosplenomegaly and the liver enzyme values had returned toward normal, despite the patient's continuing malaise. On December 29, a physical examination gave normal findings, but laboratory studies showed a leukocyte count of 2,200 per cu mm, with 154 polymorphonuclear cells per cu mm, 1,100 mature lymphocytes per cu mm, 880 atypical lymphocytes per cu mm and 66 monocytes per cu mm. The hematocrit was 39 percent; reticulocyte count, 0.6 percent; erythrocyte sedimentation rate, 7 mm per hour, and platelets were normal. A bone marrow aspirate showed normal cellularity with an increased myeloid:erythroid ratio of 4:1. There was an increase in promyelocytes and myelocytes with very few band cells or segmented neutrophils. One week later, the leukocyte count was 3,500 per cu mm, with 900 polymorphonuclear cells per cu mm, 180 band cells per cu mm, 2,170 lymphocytes per cu mm including atypical forms, and 280 monocytes per cu mm. By January 11, 1977, the leukocyte count and cell count differential were normal but the heterophil test remained positive. In April 1977, pharyngitis consistent with a mild viral infection developed, and elevation of the heterophil titer was noted (positive at 1:28). Serologic tests for EBV infection* showed an antiviral capsid antigen titer (anti-VCA, IgG) of 1:2,560 and an anti-Epstein-Barr nuclear antigen titer (anti-EBNA) of 1:40, findings consistent with a previous EBV infection.

Comment. This patient had a typical case of clinical infectious mononucleosis in December 1976. Blood smear and serology confirmed the diagnosis at that time; unfortunately, only one serum specimen was available for detailed serologic studies and was helpful only in showing previous infection by the Epstein-Barr virus.

CASE 2. Two weeks before admission to hospital, a 36-year-old woman noted an aching pain in the left posterior part of the neck associated with fatigue and malaise. Six days before admission she began having shaking chills, fevers and sweats; four days later she felt lumps on her neck.

At admission on September 2, 1977, her only complaint was of a mild epigastric pain. At home she had regularly supervised dialysis therapy for her husband, who had chronic renal failure. He was HAA (hepatitis-associated antigen) negative and had not been admitted to hospital in the previous two years. She had taken no medications except acetylsalicylic acid rarely for headaches. She gave no family history of blood diseases. In her work she was exposed to fertilizer dusts and insecticides. On examination the patient was afebrile and had shotty anterior and posterior cervical adenopathy, two small high occipital lymph nodes and a palpable spleen tip. The leukocyte count was 16,800 per cu mm with 8,400 atypical lymphocytes, 8,200 normal lymphocytes and 200 monocytes per cu mm, and no neutrophils. Hematocrit was 39 percent; reticulocyte count, 1.3 percent; platelets normal on smear; erythrocyte sedimentation rate, 33 mm per hour; SGOT, 125 units per ml, and a Monospot test was equivocally positive. Repeat Monospot test was negative and tests for toxoplasma, cytomegalovirus (CMV) herpes simplex and rubella infections were also negative. Serology for EBV infection showed anti-VCA (IgG) titer of 1:160,

*Serologic tests for Epstein-Barr virus in cases 1, 2 and 3 were done by Dr. Werner Henle, Director, Division of Virology, The Joseph Stokes, Jr. Research Institute, The Children's Hospital of Philadelphia, Philadelphia.

anti-VCA (IgM) titer of 1:640 and an anti-EBNA titer of 1:5 on September 7. Repeat titers were 1:160, 1:320 and 1:10, respectively, on September 15 and 1:80, less than 1:10 and 1:20, respectively, on October 12.

Blood smears showed rare neutrophils over the next three days. A marrow study on September 6 showed myeloid hyperplasia with normal maturation to band forms. At that time a few segmented neutrophils were identified on a blood smear. On September 15 the leukocyte count was 7,000 per cu mm, with 460 polymorphonuclear cells per cu mm, and the patient was clinically improved. Weekly blood counts showed continuing resolution of the granulocytopenia, and the patient reported that the symptoms were completely gone by October 12.

Comment. This patient had a clinically atypical case of infectious mononucleosis. Our initial hypothesis that her illness might be due to toxoplasma, CMV, herpes simplex, or rubella infection could not be confirmed serologically. The diagnosis of EBV infection is based on characteristic serologic changes of a recent primary EBV infection. The falling titer of IgM antibody to viral capsid antigen (anti-VCA, IgM) and rising titer of antibody to Epstein-Barr nuclear antigen (anti-EBNA) are sequential changes diagnostic of recent EBV infection.[5,6]

CASE 3. In a 32-year-old man sore throat, malaise, myalgias and headaches developed in December 1974. The symptoms persisted until March 1975 when he was first seen by a physician, who noted tender cervical adenopathy and an injected pharynx but no hepatosplenomegaly. The leukocyte count was 6,600 per cu mm, with 3,300 neutrophils, 2,000 atypical lymphocytes and 660 monocytes per cu mm. A Monospot test was positive.

The patient's symptoms persisted until April 17 when he noted increased sore throat and headache without fever or chills. He said he had taken no drugs except acetylsalicylic acid and chlorpheniramine, and he did not recall exposure to other known toxins. On physical examination the man appeared acutely ill. Temperature was 39.4°C (103°F), there was severe exudative pharyngitis, and tender cervical and submandibular adenopathy, without hepatosplenomegaly. Laboratory studies showed a hematocrit of 35.3 percent; hemoglobin, 12.0 grams per dl; reticulocyte count, 0.2 percent, and platelet count, 109,000 per cu mm. The leukocyte count was 1,000 per cu mm, with 940 lymphocytes which were predominantly atypical, 40 monocytes and 20 basophils per cu mm. A marrow aspirate showed a substantial decrease in the number of myeloid elements with only rare myeloblasts and promyelocytes and no segmented granulocytic elements.

Other laboratory tests showed a bilirubin value of 1.3 mg per dl with normal SGOT, lactic dehydrogenase (LDH) and alkaline phosphatase levels. Repeat Monospot test was positive again and serology for CMV was negative. Serology for EBV infection gave an anti-VCA (IgG) titer of 1:40 and an anti-EBNA titer of less than 1:2 on April 19. On May 1, repeat values were 1:160 for anti-VCA (IgG) and 1:10 for anti-EBNA.

After collecting specimens for culture (all cultures subsequently were negative), administration of penicillin and gentamicin was begun. Fever and agranulocytosis persisted through hospital day 4 with the total leukocyte count remaining less than 2,000 per cu mm and no polymorphonuclear cells seen on smear. On day 5 the total leukocyte count rose to 2,100 per cu mm and 7 percent polymorphonuclear cells were noted. At this time the patient's fever abated and antibiotic therapy was discontinued. By day 8 the total leukocyte count had risen to 5,300 per cu mm with 1,800 neutrophils per cu mm; hematocrit, 38 percent, and platelets, 421,000 per cu mm. The patient was discharged. Over the next three months malaise and fatigue persisted but adenopathy gradually resolved. Occasional atypical lymphocytes persisted on peripheral smear for up to four months after discharge.

Comment. This patient's illness was also unusual for infectious mononucleosis. His prolonged prodrome was not well documented and may have been a separate illness. At the time of the first evaluation in March 1975, the patient appeared to have infectious mononucleosis. The subsequent detailed serologic changes are consistent with a primary EBV infection.

Discussion

The occurrence of mild decreases in granulocyte counts early in infectious mononucleosis was first documented in the classic monograph by Downey and McKinlay.[7] Later studies supported the occurrence of this phenomenon, showing that a fall in total circulating granulocyte numbers regularly occurred in up to 40 percent of cases

during the first and second weeks of illness.[8,9] Although several case reports have suggested that severe, life-threatening granulocytopenia may occur with infectious mononucleosis,[11,14,18,19,21-27] concurrent drug or toxin exposures and incomplete reporting of case data make interpretation of the relationship difficult.

The diagnosis of infectious mononucleosis is based on the clinical pattern of illness, atypical lymphocytosis in the blood and the presence of heterophil agglutinins in the serum. In a small proportion of patients with clinical features of mononucleosis, heterophil agglutinin tests have been reported as negative. Although a few of these patients with heterophil-negative mononucleosis syndromes may actually have heterophil agglutinins demonstrable with horse erythrocyte reagents rather than with sheep erythrocyte materials, in some more sophisticated serologic testing is required. Specific tests for antibody to EBV-induced antigenic determinants can differentiate mononucleosis syndromes due to cytomegalovirus from those due to the Epstein-Barr virus.[6] Although in our patients there were variable clinical manifestations of the mononucleosis syndrome, in all three large numbers of circulating atypical lymphocytes were seen on blood smear. In two of our patients there were heterophil agglutinins with appropriate differential absorption patterns (cases 1 and 3) while a study in the third was negative. In this latter patient the EBV-specific serologic tests showed serial changes similar to those reported previously in patients with heterophil-negative infectious mononucleosis due to the Epstein-Barr virus.[6]

The three cases we have presented showed severe neutropenia in association with serologically well-documented infectious mononucleosis syndromes due to the Epstein-Barr virus. The pattern of onset in relation to the viral infection, duration of severe neutropenia and recovery of blood counts suggested the possibility that the EBV caused the decreased counts. Other causes of severe neutropenia such as drug or toxin exposure appear unlikely in our cases because each patient either inadvertently continued to take the potential agent (meprobamate, case 1) or was reexposed by returning to work (cases 2 and 3) or taking the nonprescription drug again (acetylsalicylic acid and chlorpheniramine, case 3) without evident harm.

The cases of severe neutropenia (less than 200 per μl) from the literature show that the temporal and morphologic findings we have noted are not peculiar to our patients (see Table 1). Six of the eight case reports from the literature that had adequate data for review showed almost identical marrow histology with a prominence of promyelocytes (with or without myelocytes) and a decrease in or lack of more mature neutrophils; the remaining two case reports showed myeloid hyperplasia. The time course of the neutropenia was also similar among the cases, confirming the impression that this extreme neutropenia is a self-limited process and suggesting a causal relationship. In each case acceptable serologic data are provided to support the clinical diagnosis of infectious mononucleosis. Several possible cases were omitted for lack of sufficiently detailed reports.[10(cases 1 and 2),11(case 1),12-20]

Detailed review of the cases of severe neutropenia in Table 1 shows several common features. First, the age and sex distributions are usual for infectious mononucleosis except for case 10. Second, the onset of severe neutropenia occurs from 14 to 40 days after symptoms begin, generally later than the previously noted mild granulocytopenia. Third, the time course of the neutropenia is extraordinarily predictable: in eight of the nine patients who recovered, the granulocyte count exceeded 500 per μl within 3 to 7 days, and in the two patients who died, the supervening fatal bacterial infections (Staphylococcus aureus in both cases) occurred very soon after discovery of neutropenia, at 1½ and 3 days. Fourth, in three of these 11 cases (cases 2, 9 and 10) myeloid hyperplasia was noted, while in the remaining eight, promyelocytes and myelocytes were present or increased and more mature neutrophilic cells were depleted.

In our patients bone marrow studies showed intact populations of promyelocytes and myelocytes with a relative or absolute decrease in mature neutrophils in two patients and myeloid hyperplasia in the third; these findings might be seen in several different situations. The term *maturation arrest* was used for these marrow findings in cases 4, 5 and 8 from our literature review. However, the fact that the blood counts generally returned to normal within five to seven days suggests that the marrow findings represent a proliferative response to an earlier marrow cell injury. The repeat marrow aspirates in case 11 support this view. Although we have no evidence at present as to the pathophysiology of the severe neutropenia in these persons our review of the

TABLE 1.—*Clinical and Laboratory Data in 11 Patients With Infectious Mononucleosis and Severe Neutropenia*

Case	Age (Years)	Sex	Time* (Days)	Lowest Leukocyte Count (cells/μl)	Lowest PMN Count (cells/μl)	Duration of Neutropenia (Days)	Hematocrit/Platelet Count (per cu mm)	Bone Marrow Findings	Serology	Drug Exposure	Therapy and Comments
Present Series											
1	16	F	34	2,200	154	7	39 percent/normal	Pronounced increase of promyelocytes and myelocytes	HA+	Meprobamate	Lived; no alteration of meprobamate dosage, no other drug exposure
2	36	F	16	7,000	0	11	40 percent/238,000	Myeloid hyperplasia, normal maturation	See text	Insecticide and fertilizer dusts	Lived; no corticosteroids, no antibiotics, no other drug exposure
3	32	M	40	1,000	0	5	35 percent/109.000	Absence of myeloid elements beyond the promyelocytes; relatively normal erythroid and megakaryocyte series	Monospot+	Acetylsalicylic acid, chlorpheniramine, paint fumes	Lived; antibiotics; leukoagglutinins negative; persistent symptoms and atypical lymphocytes
Literature Series											
4	19	M	32	3,800	38	3	34 percent/170,000	Normal erythroid and megakaryocytic lines; block of maturation beyond promyelocyte	Paul Bunnell +1:640	Pyramidon (aminopyrine), Salgydal	Lived; treated with hydrocortisone for Guillain-Barré syndrome before neutropenia; no leukocyte antibodies found[28]
5	19	F	26	2,000	0	7	34 percent/103,000	Complete arrest of promyelocytes with normal erythroid and megakaryocyte series	HA+1:128	Before onset of symptoms, none; at onset of symptoms: penicillin, tetracyline; phenacetin, codeine, acetylsalicylic acid	Lived; treated with prednisone after agranulocytosis diagnosed; leukoagglutinins negative; sister died of leukemia at age 5 years[23]
6	19	M	20	3,400	0	5	NR	Absence of mature polymorphonuclear cells; increased promyelocytes and myelocytes; normocellular	Monospot+	At onset of symptoms: acetylsalicylic acid, penicillin	Lived; treated with prednisone and nonabsorbable oral antibotics; leukoagglutinins negative; 18 percent atypical lymphocytes after 83 days[24]
7	29	M	14	1,800	0	3	44 percent/204,000	Normocellular, no cells beyond promyelocyte	HA+1:896	NR	Lived; treated with oxacillin, gentamicin and prednisone after neutropenia diagnosed; leukoagglutinins negative; 10 percent atypical lymphocytes after 60 days[11]
8	35	F	40	2,200	0	3	40 percent/133,000	Late maturation arrest of myeloid series	HA+ >1:4,000	Mefenamic acid; barbiturates	Lived; treated with penicillin and pethidine after neutropenia diagnosed; persistent headache and abnormal cerebrospinal fluid for months after; jaundice[25]
9	24	M	15	6,500	0	1½	35 percent/ 78,000	Myeloid hyperplasia, maturation normal	Ox cell hemolysin titer+ 1:960	At onset of symptoms: penicillin	Died of Staphylococcus aureus pneumonia with acute respiratory distress syndrome; had been treated with penicillin, methicillin; no corticosteroids given[27]
10	2	M	20	2,700	162	3	37 percent/ 96,000‡	Myeloid hyperplasia, adequate megakaryocytes	HA+1:224 Monospot−	At onset of symptoms: ampicillin	Died; S. aureus and Hemophilus influenzae in blood, pneumonia and Reye syndrome; had been treated with ampicillin for three doses, then cephalothin and gentamicin for three days; no corticosteroids given; two uncles died of leukemia in childhood[26]
11	19	M	23	1,500	0	6	NR†/NR	Myeloid hypoplasia, with only promyelocytes seen initially; four days later, marrow myeloid hyperplasia	HA+1:896	At onset of symptoms: penicillin and sulfadiazine	Lived; treated with sulfonamides four months before illness; penicillin during neutropenia; no corticosteroids given[22]

HA = heterophil agglutinin NR = not recorded PMN = polymorphonuclear cell + = reported as positive

*Time from onset of symptoms to onset of neutropenia. †Hemoglobin is 14.8 grams per dl. ‡Initial count; count fell to 11,000 per cu mm just before death.

data shows that severe neutropenia can be an important complication of infectious mononucleosis. Until the pathogenesis of this complication is clearly understood, and early or preventive treatment shown to be useful, we recommend close observation of these patients and early treatment of suspected superinfections.

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Use of Metronidazole (Flagyl) Contraindicated in First Trimester of Pregnancy

WHAT IS THE TREATMENT of trichomoniasis in pregnancy? Animal data suggest that metronidazole (Flagyl) is contraindicated during the first trimester and is probably safe during the second and third trimesters. I would try to avoid it, if possible, all the time during pregnancy. If a woman comes in during the first trimester with trichomoniasis, I will treat her with local therapy. I prefer to use vinegar douching—two tablespoons of vinegar in a quart of warm water—and instruct her how to douche in pregnancy; you have to do it very gently. The reason I prefer that is that it restores the normal pH of the vagina; it is essentially antagonistic to the trichomonas; and it does not distort normal vaginal flora.

—MICHAEL F. REIN, MD, *Charlottesville, Virginia*

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