

THE DIAGNOSIS AND TREATMENT OF ACUTE AGRANULOCYTOSIS

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PROMPT recognition of acute agranulocytosis is important because early and adequate treatment will effect a complete recovery in about 90 per cent of the patients. Penicillin, and to a lesser extent other antibiotics and chemotherapeutic drugs, have reduced materially the former high mortality rate.

The severity of the disease is demonstrated by the initial report of Schultz¹ in 1922 in which 5 fatal cases were described, each characterized by extensive ulcerations of the mouth and pharynx, fever, and a pronounced decrease of the white blood cell count. He observed the profound diminution of the polymorphonuclear leukocytes and the total absence of these cells from the peripheral blood and suggested the name agranulocytosis. This report created world-wide interest and recognition of the clinical syndrome although Brown² in this country is credited with the first authentic case report in 1902.

The term "agranulocytic angina" was introduced in 1923 and is generally accepted. Some of the more common synonyms include malignant leukopenia, granulopenia, and toxic myelosis. The latest edition (1942) of the Standard Nomenclature of Diseases of the American Medical Association recommends the name "acute agranulocytosis" under the inclusive term granulocytopenia.

Clinical Manifestations

The onset of the disease is usually abrupt but may be preceded by headache, malaise or mild prostration for 1 or 2 days. It has been shown that depression of the white blood cell count due to a decrease in the granulocytes occurs prior to the onset. The symptoms are usually sore throat, difficulty in swallowing, and fever indicative of infection. The physical examination reveals an acutely ill patient with temperature ranging from 101 F. to 103 F., rapid pulse, and often mild delirium. The oral mucous membranes including the fauces, gums, tongue, and pharynx show multiple superficial ulcerations covered with a tenacious brown exudate. The tonsils and other lymphoid tissue in the pharynx are red, swollen, and may show evidence of necrosis. Cervical lymphadenopathy is frequently observed although generalized lymphadenopathy is absent. The spleen is rarely palpable. The liver is seldom enlarged but jaundice may occur in critically ill patients as a result of the severe infection and is generally a deterrent to recovery. If unusual pallor is observed suggesting an anemia, some doubt must be entertained concerning the accuracy of the diagnosis.

Etiology

In 1932, Kracke³ reported the production of a severe granulocytopenia in rabbits receiving subcutaneous injections of benzene in olive oil. He stated that the cause of acute agranulocytosis was unknown but that the benzene ring must be given strong consideration. Madison and Squier⁴ in 1934 conclusively demonstrated that amidopyrine was the cause of the disease in 14 patients. They were able to show a prompt and temporary depression of the granulocytes following the oral administration of 0.3 Gm. of amidopyrine to 2 patients who had recovered from the disease. These facts were later confirmed by others.

Arsphenamine and neoarsphenamine may cause acute agranulocytosis but more often these drugs produce a toxic marrow depression with anemia, leukopenia and thrombopenia. Fortunately, these reactions were uncommon except during the era of rapid arsenotherapy. Shortly after the introduction of the sulfonamide drugs, it was established that agranulocytosis may follow the use of sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and sulfamerazine. Even sulfaguanidine and succinyl sulfathiazole, which are absorbed poorly from the gastrointestinal tract, can cause this disease. This observation is of interest in view of the experimental production by Daft⁵ of a profound granulocytopenia in rats fed a purified diet and succinyl sulfathiazole successfully treated with folic acid. Theoretically, it is believed that the synthesis of folic acid in the intestinal tract is impaired by the alteration of the bacterial flora resulting from the succinyl sulfathiazole.

Gold, widely used in the treatment of rheumatoid arthritis, is another therapeutic agent capable of causing agranulocytosis. However, such reaction is uncommon. Toxic reactions are more apt to occur as high total dose levels are approached. Dinitrophenol was soon withdrawn from the accepted drug list because of this and other toxic effects. To date, no convincing reports have been published on tridione or mesantoin as causes of agranulocytosis. These new anticonvulsant drugs are not without toxic effects however as several reports have confirmed the production of an aplastic anemia following their use. Within the past year, 2 patients have been observed at the Cleveland Clinic Hospital with anemia, leukopenia, and hypoplastic bone marrow due to mesantoin. Both recovered.

With the advent of the antithyroid drugs it became evident that thiouracil, methyl thiouracil, and propyl thiouracil were capable of producing agranulocytosis. Thiouracil is considerably more toxic in this respect than the later derivatives. Propyl thiouracil and methyl thiouracil rarely give rise to a serious granulocytopenia if excessively large doses are not employed. In a group of 450 patients treated with propyl thiouracil at the Cleveland Clinic, none developed agranulocytosis.⁶

The following drugs have been suspected of causing agranulocytosis but conclusive proof is lacking: barbiturates, phenacetin, quinine and quinidine, cincophen, bismuth, and plasmoquin.

Blood and Marrow Observations

There may be a mild anemia of a normochromic or hypochromic type but if any appreciable reduction of the hemoglobin, red blood cell count, or platelets is present, the accuracy of the diagnosis is questionable. The characteristic feature is a severe depression of the total white blood cell count (leukopenia) with a relative decrease of the polymorphonuclear leukocytes (granulocytopenia). The lymphocytes and monocytes show no consistent change in number nor morphology. The granulocytes are usually below 20 per cent, often 10 per cent, and not infrequently they may be entirely absent. The granulocytes often show basophilic granulation which is considered a toxic effect. Repeated blood counts are important in order to record the progress of the patient. A significant increase of granulocytes in the peripheral blood often indicates a clinical recovery may be expected. (These features are noted in the series observed at the Cleveland Clinic—Table).

Following observation of the bone marrow changes in several fatal cases Fitz-Hugh and Krumbhaar⁷ proposed the concept of a maturation arrest of the granulocytic cells at the myelocyte stage of development. Others have confirmed by sternal puncture technic the presence of ample granulocytic cells up to and including myelocytes, and the virtual absence of metamyelocytes and mature granulocytes. The observations vary according to the stage of the disease but myeloid hyperplasia is recognizable during the acute phase. There is no disturbance of erythropoiesis and the megakaryocytes appear normal.

Case Reports

Case 1. A 29-year-old physician consulted Dr. Russell Haden⁸ in December, 1933, and gave a history of recurring attacks of chills, fever, stomatitis, and pharyngitis. In each attack a leukopenia with relative decrease in the granulocytes was observed. The first episode occurred in September, 1932, and during the ensuing 15 months, he had 8 recurrent attacks. Further history revealed that these attacks were preceded by migraine headaches from which relief was sought by the use of amidopyrine, 0.6 to 0.9 Gm. (pyramidon), allonal (containing amidopyrine), and acetylsalicylic acid. Repeated blood counts showed no evidence of anemia. The total white blood cell count varied from 1500 to 3000 per cu. mm. with the polymorphonuclear leukocytes comprising 4 to 15 per cent. All drugs containing amidopyrine were stopped and no further attacks recurred during the following 4 years, while subsequent blood counts have remained normal.

Case 2. A 48-year-old salesman was referred to the Cleveland Clinic on June 21, 1949, with the chief complaint of sore throat. The present illness began abruptly 10 days prior to admission, characterized by sore throat, fever, and swollen cervical glands. During the 6 days prior to admission, he received daily injections of 300,000 units of penicillin without appreciable clinical improvement and his fever and stomatitis continued. No blood counts were performed prior to admission. The past history disclosed that a diagnosis of diffuse toxic goiter and coronary heart disease had been established in 1947. Treatment at that time was started with thiouracil, 0.9 Gm. daily, in repeated courses of 2 to 3 weeks' duration. The last course was instituted 2 weeks prior to the onset of the present illness and several tablets were prescribed the day before admission to the Clinic.

ACUTE AGRANULOCYTOSIS

TABLE

Age	Sex	Total W.B.C. Count	P.M.N. (%)	R.B.C. Million Per Cu.Mm.	Hb. %	Drug	Treatment	Result
65	M	400	4	3.86	65	Allonal Aminopyrine	Transfusion Pentnucleotide	Died
59	F	750	4	4.2	78	?	Transfusion Liver extract	Recovered (several attacks)
68	F	2650	0	4.8	75	Sulfathiazole	Transfusions Penicillin Liver extract	Recovered
48	M	2050	20	4.7	94	Thiouracil	Penicillin Streptomycin Liver extract Folic acid	Recovered
46	F	250	10	4.55	68	Aminopyrine	Transfusions Liver extract	Recovered
52	F	600	0	4.0	80	?	Transfusions	Died
29	M	2200	8	4.6	95	Aminopyrine	Pentnucleotide Transfusion Liver extract	Recovered (several attacks) Migraine
59	F	1200	12	4.9	84	Aminopyrine	Sulfathiazole	Recovered

Physical examination revealed an acutely ill patient with a fever of 102.2 F., pulse of 120, and a thick gray exudate over the oral mucous membranes and pharynx beneath which multiple small ulcerations were observed. The tonsils showed several necrotic ulcers. The cervical lymph nodes were enlarged and tender but there was no generalized lymphadenopathy. There was no icterus, purpura, nor dermatitis. The liver and spleen were not palpable. The previous clinical diagnoses of diffuse toxic goiter and coronary heart disease were confirmed by later studies.

On admission, the hemoglobin was 14.5 Gm., red blood cell count 4,730,000 per cu. mm., white blood cell count 1500 per cu. mm., with 20 per cent granulocytes, 66 per cent lymphocytes, and 14 per cent monocytes. Most of the granulocytes were mature although several myelocytes and metamyelocytes were observed. The polymorphonuclear leukocytes showed severe basophilic (toxic) granulation. Sternal puncture disclosed a cellular marrow with normal erythropoiesis and myeloid hyperplasia. The striking feature was the noticeable increase of myelocytes and conspicuous reduction of mature granulocytes. Blood cultures remained sterile. Other studies, including roentgen examination of the chest, were normal.

The initial procedure in treatment was the cessation of thiouracil. The penicillin was continued and increased to 600,000 units daily. Dihydrostreptomycin, 1 Gm. daily, in divided doses was given parenterally until recovery 7 days later. In addition, he received 6 cc. of liver extract intramuscularly and parenteral crystalline folic acid in 10 mg. doses three times each day. The stomatitis and pharyngitis gradually improved and he was afebrile on the seventh hospital day. Prior to discharge, the white blood cell count was 12,250 per cu. mm. with 70 per cent granulocytes. His convalescence was uneventful and radioactive iodine was advised for the treatment of his hyperthyroidism.

The patient was seen in the later stage of acute agranulocytosis and it appears that the empiric use of penicillin prior to recognition of the diagnosis prevented a fatal result in spite of continuation of the thiouracil.

Differential Diagnosis

Agranulocytosis is a brief illness with an acute onset occurring primarily in adults. The stomatitis, pharyngitis, and mucosal ulcerations are also present in such conditions as acute leukemia, acute aplastic anemia, diphtheria, Vincent's angina and other local infections. Characteristic changes in the peripheral blood and bone marrow in agranulocytosis have been discussed. It is usually possible to obtain a history of the use of some drug capable of causing the disease prior to the acute onset. In general, the absence of generalized lymphadenopathy, splenomegaly, pallor, or purpura aid in the differential diagnosis of acute agranulocytosis.

The conditions most likely to present difficulties in the differential diagnosis are acute leukopenic leukemia and acute toxic aplastic anemia. In these diseases, anemia and thrombopenia are seldom absent. In leukopenic leukemia, careful study of the blood smears will reveal the presence of "blasts." This study is facilitated by preparation of a concentrated smear of the "buffy coat" from the hematocrit tube which contains primarily the white blood cells. Bone marrow studies obtained by sternal or iliac crest puncture often give conclusive proof of the diagnosis in these diseases.

Treatment

The prevention of acute agranulocytosis is perhaps possible to a limited extent but is difficult in view of the abrupt onset. The physician's awareness of the various drugs capable of producing this reaction is important. It has been shown that only a small percentage of patients develop this complication as a result of these drugs. There appears to be no adequate explanation for the infrequent observation of acute agranulocytosis during the period 1902 to 1925, as pyramidon (amidopyrine) was widely used following its introduction from Germany in 1902. There is no convincing evidence that allergy plays a role. The reaction appears to be a drug sensitivity in susceptible persons.

In the clinical use of the sulfonamides and antithyroid drugs which are administered daily over a period of time, instruction of the patient to report promptly any symptom indicative of this complication is probably the most important feature in its prompt recognition. Progress blood counts may be of some value depending on the relative toxicity of the drug employed. With the constant influx of new drugs on the market, the possibility of granulocytopenia should be kept in mind as these reactions may not have been observed in animal experiments nor preliminary clinical trials. For example, Blanton and Owens⁹ recently reported a case of acute agranulocytosis in an elderly woman receiving 200 mg. of pyribenzamine daily for the treatment of urticaria. They believed this was the offending agent but hesitated to administer the drug in a clinical trial following the recovery of the patient. Additional evidence is presented that pyribenzamine may cause agranulocytosis by the case report of Cahan and his associates.¹⁰ They cite personal knowledge of a similar reaction to this antihistaminic drug. In these 3 patients the drug was taken for several weeks prior to the onset of the agranulocytosis.

As soon as the diagnosis of acute agranulocytosis is established or strongly suspected, the offending drug should be determined and its administration stopped. Vigorous measures for the control of the infection are essential and since the advent of penicillin, it is the agent of choice. It is suggested that minimal parenteral doses of 600,000 units be given daily until the patient recovers. Depending on the clinical condition of the patient and bacteriologic studies, streptomycin, chloramphenicol, or aureomycin may be required as supplementary measures.

Sulfonamide drugs, especially sulfadiazine, were often effective in controlling the infection but have been largely replaced by the less toxic antibiotics. In the treatment of agranulocytosis due to the heavy metals such as gold or arsenic, the use of BAL is recommended in conjunction with agents to control infection.

Conservative treatment of the oral lesions is advisable and consists of warm saline irrigation and applications of mild antiseptics. The topical application of penicillin to the mucous membranes is of dubious value.

Blood transfusions may be useful in correction of mild anemia and as a general supportive measure. There is little proof that the transfused leukocytes cause more than a transient rise in the white blood cell count of the recipient.

If transfusions are given, whole freshly drawn blood is probably better than "banked" blood.

It is believed that a large percentage of patients will recover if the infection is effectively controlled during the period of granulocytopenia which often lasts for 5 to 8 days. The return of granulocytes in the peripheral blood is apparently spontaneous. In view of the experimental evidence in animals that granulocytopenia due to the sulfonamides and antithyroid drugs is benefited by folic acid, this agent has been advocated and generally used in recent years. Theoretically, it appears sound to give 10 to 20 mg. of folic acid parenterally several times daily, although clinical proof of its exact value is difficult to establish.

Pentnucleotide therapy is not recommended.

Summary

The clinical and hematologic features in acute agranulocytosis have been discussed and the present concept of treatment outlined.

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