Syndrome of Hypogammaglobulinemia, Splenomegaly and Hypersplenism

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SINCE THE REPORT of Bruton[1] many cases of a gammaglobulinemia or hypogammaglobulinemia have been reported in the literature. Three forms of this metabolic disturbance have been described:[2] (a) a physiologic or transient form occurring in infants; (b) a congenital form; and (c) an acquired form. It has also been shown that the failure of gamma globulin synthesis in congenital and acquired types, is not complete and that small amounts of serum gamma globulin may be demonstrated by sensitive technics. As such the term hypogammaglobulinemia has been used in this paper. Prasad and Koza[3] described the first instance of this disorder complicated by hypersplenism and hemolytic anemia. No specific cause for the splenomegaly was found and it was postulated that it was due to reticuloendothelial system hyperplasia which in turn was related to the basic disorder, namely the lack of gamma globulin. Recent reports[4-15] appear to confirm this observation. This syndrome is believed deserving of recognition with special reference to appropriate management. It is the purpose of the present paper to describe an additional case of acquired idiopathic hypogammaglobulinemia complicated with acquired hemolytic anemia and splenomegaly, to report on the follow-up of the first case,[3] and to review the literature.

Case Reports

Case No. 1, E. H. U. H. #901539. This 65 year old white female was admitted for the first time to the University Hospital on August 2, 1956. The patient was well until 1949 when her illness started. Within the past seven years she had twelve episodes of pneumonia. She developed anemia and weakness and her local physician noted splenomegaly. She received liver therapy, B_{12} and iron for anemia with little response. On September 13, 1955, her hemoglobin was 10.7 grams % and total leukocytes were 4,650 per cu. mm. Reticulocyte count was 7.2%. In December 1955 she was given prednisone 5 mg. four times a day. In March 1956 blood transfusions became necessary and she received 25 pints of blood during the past five months prior to admission. Eleven pints were transfused during the past 16 days prior to admission. Family history was unremarkable. Physical examination (on admission): Temperature 100.4 F., pulse 140, B.P. 126/55. Purpura were present on both forearms. Sclerae were icteric. Bilateral basilar rales were present. The heart was enlarged to the left by percussion and a soft apical systolic murmur was present. Liver was palpable 5 cm. below the right costal margin and the spleen was firm and extended to the level of the left iliac crest. Moderate pitting edema of the lower extremities was observed.

Laboratory data: Hemoglobin 4.2 grams per 100 ml., RBC 131 millions per cu. mm., total leukocytes 2100 per cu. mm., neutrophils 32%, lymphocytes 60%, monocytes 6%, eosinophils 1% and basophils 1%. Hematocrit 13%, reticulocyte count 5.4%, platelets 53,000 per cu. mm., bleeding time, clotting time and prothrombin time were within normal limits. Routine urinalysis revealed a trace of albumin and occasional WBC. Erythrocyte sedimentation rate 100 mm. in one hour. BUN 17 mg. %, serum bilirubin 1.0 mg. in one min. and total 3.1 mg. (bilirubin ratio 32%). Total serum proteins 4.5 grams %, albumin 3.3 grams %

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and globulins 1.2 grams %. Zinc turbidity 1 unit. Alkaline phosphatase 17.2 KA Units. Fecal urobilinogen 855 mg. per 100 grams of stool or 658 mg. per day. Serum iron was 163 μg. %. Blood cultures were sterile. Cold agglutination test was negative. Direct Coomb's test was negative. Indirect Coomb's test was negative with cde cells but was positive with CDE cells probably due to previous transfusions. Blood group was O Rh positive. Chest x-ray revealed pleural reaction and/or small amount of fluid in the right costophrenic angle.

Paper electrophoresis revealed albumin 3.2 grams, alpha-1 globulin 0.4 Gm., alpha-2 globulin 0.5 Gm., beta globulin 0.7 Gm. and gamma globulin 0.6 Gm. %. Normal gamma globulin for our laboratory is 1.1 Gm. ± 0.3 Gm. The distinctly low value despite recent blood transfusions indicated that the patient had acquired hypogammaglobulinemia. This correlated well with the very low zinc turbidity. Presumably the amount of gamma globulin, though considerably reduced, was sufficient to account for the positive indirect Coomb's test. (See above.) Bone marrow findings were compatible with a severe hemolytic anemia of the acquired type. No evidence of other blood dyscrasia was found. L.E. clot test was negative.

In spite of prednisone 75 mg. daily for a week and five pints of blood transfusion, the hemoglobin fell to 5 Gm. %. At this point, splenectomy was believed to be necessary. The patient was transfused to 13 Gm. % of hemoglobin and splenectomy was performed on the eleventh hospital day. Total leukocytes ranged between 3,000 to 3,900 per cu. mm. prior to surgery. Fourteen ml. of gamma globulin were administered at the time of surgery.

Postoperatively the patient did reasonably well except for urinary tract infection which responded to antibiotics. On the first postoperative day the patient received one pint of blood following which the hemoglobin was 12.6 Gm. %. During the first week following operation, the total leukocytes ranged between 5500-9900 per cu. mm. and the platelet count was 178,000 per cu. mm. The spleen weighed 740 Gm. Microscopic examination of the spleen and the liver biopsy failed to reveal any evidence of leukemia or any other related process. The changes were compatible with those of acquired hemolytic anemia. Cortisone was discontinued on the sixth postoperative day and the patient was discharged on the eleventh postoperative day. Administration of gamma globulin at intervals of three weeks and also antibiotics in case of any definite infection was advised. She did not require any blood transfusion and the hemoglobin did not fall below 11.5 Gm. %. On October 19 she was admitted to her local hospital with bilateral pneumonia and expired on October 29, 1956. Unfortunately an autopsy was not performed.

Case No. 2, L. L. Ancker Hospital (St. Paul) No. A-172630. This is a follow-up of the first reported case[3] of this syndrome. This 30 year old white female was found to have hypogammaglobulinemia in December 1953. The history of recurrent infections dated back to 1944. The spleen was found to be enlarged for the first time in 1947. The patient developed hepatosplenomegaly, lymphadenopathy, hemolytic anemia, leukopenia and thrombocytopenia. Hypersplenism was diagnosed and splenectomy was performed in May 1952. Examination of the spleen and a lymph node biopsy revealed nonspecific granulomata and reticulum cell hyperplasia. The patient's ninth hospital admission to Ancker Hospital was in November 1953 for meningitis. The physical examination on admission revealed: temperature 101 F., pulse 110 and blood pressure 144/80. The patient was a well developed and well nourished white female. Positive findings were rigid neck, positive Kernig's sign, scattered rales in the left lower lobe and right middle lobe of the lung and generalized lymphadenopathy. The clinical diagnosis was meningitis. The cerebrospinal fluid smear was positive for D. pneumoniae and blood culture was positive for the same organism. She was treated with aqueous penicillin 400,000 units every four hours, sulfadiazine 1 Gm. every four hours and terramycin 500 mg. every six hours and became afebrile after four days of therapy. Because of the history of repeated infections, an electrophoresis of the serum proteins was obtained and diagnosis of hypogammaglobulinemia was established. The values obtained for the fractions of the serum proteins were: albumin 3.7 Gm., alpha-1 globulin 0.6 Gm., alpha-2 globulin 0.6 Gm., beta globulin 0.7 Gm., gamma globulin 0.0 %.

A few other features of this case are worthy of emphasis. The sedimentation rate remained low most of the time in spite of acute infections. Similar observations have been reported by others in cases of hypogammaglobulinemia.[6, 13, 20] Unfortunately, fibrinogen determinations have not as yet been made or reported by others during episodes of infec-

tions. The blood group was O Rh positive. Agglutination tests and skin tests for tuberculosis and triple fungi were negative.

After the diagnosis of hypogammaglobulinemia was established the patient was started on gamma globulin therapy and prophylactic antibiotics. However, the gamma globulin administration was discontinued after approximately four months and she was maintained on penicillin 200,000 units twice daily and aureomycin 250 mg. four times daily orally. In October 1954 the patient delivered a normal baby girl. From August 1955 to mid-October 1955 she received only oral penicillin. On October 16, 1955, she was admitted to the hospital for bronchopneumonia. She was treated with penicillin 400,000 units I.M. and terramycin 250 mg. orally every six hours with good results. Pertinent laboratory data on this admission revealed the following: Hemoglobin 12 Gm. %, total leukocytes 13,600 per cu. mm., reticulocyte count 1.6 %, erythrocyte sedimentation rate 3 mm. per hour. The total leukocytes were 9,000 per cu. mm. prior to discharge. The patient was discharged on October 28, 1955. She was advised to continue penicillin and terramycin. Since her last discharge she has done well. At present she is on penicillin 200,000 units twice daily and terramycin 250 mg. four times daily orally. Protein determinations on this patient are shown in table 1.

Comments: This patient is an example of acquired hypogammaglobulinemia and hypersplenism. The history indicates that hypogammaglobulinemia definitely preceded the onset of splenomegaly and hypersplenism. The granulomas observed were probably due to repeated infections as a result of hypogammaglobulinemia.

TABLE 1

Date	Total Serum Protein in Gm. %	Albumin in Gm. %	Globulin in Gm. %
2-5-51	5.80	4.64	1.16
12-15-51	6.20	4.56	1.64
12-1-53	5.55	4.76	0.79
12-5-53	5.50	4.56	0.94
10-25-55	6.85	5.00	1.85

TABLE 2.—*Cases of Acquired Idiopathic Hypogammaglobulinemia, Splenomegaly and Hypersplenism*

Authors	Year	# of Cases Reported	Anemia	Leukopenia	Thrombocytopenia
Prasad and Koza[3]	1954	1	Present	Present	Present
Prasad et al	1956	1	Present	Present	Present
Rohn et al.[4]	1955	1	Present	Present	
Grant and Wallace[5]	1954	1	Present	Present	
Brem and Morton[6]	1955	3			
Collins and Dudley[7]	1955	1	Present	Present	
Young et al.[8]	1955	1			
Rosecan et al.[9]	1955	2		Present in one	
Standaert and DeMoor[10]	1955	1	Present	Present	Present
Ramos[11]	1956	1	Present	Present	
Martin et al.[12]	1956	1	Present	Cyclic Neutropenia	
Wechsler[13]	1956	1			
Baran dun et al.[14]	1956	1		Present	
Brückel et al.[15]	1956	1	Present	Present	Present

Splenomegaly was present in every instance.

Discussion

Rohn et al.[4] reported the case of a male with acquired hypogammaglobulinemia and acquired hemolytic anemia associated with splenomegaly. A diagnosis of hypersplenism was made and splenectomy was performed. Examination of the spleen revealed a marked increase in highly phagocytic clasmatocytes containing great numbers of phagocytized red cells, platelets and leukocytes. No other cause for splenomegaly was found. They concluded that hypogammaglobulinemia caused a compensatory hyperplasia and hyperfunctioning of phagocytic elements of reticuloendothelial system in response to infection. The patient responded well to splenectomy and has been maintained on gamma globulin therapy subsequently. Grant and Wallace[5] reported the case of a 17 year old girl who had hypogammaglobulinemia, splenomegaly and leukopenia. The hemoglobin was slightly low (11.8 Gm. per cent) but further data with relation to possible hemolytic anemia were not given. Since no other cause of splenomegaly was found, the authors concluded that it was a result of compensatory reactive hyperplasia of the reticuloendothelial system, due to lack of gamma globulin. The leukopenia and presumably the anemia was due to hypersplenism. Brem and Morton[6] have also stressed this feature. Three of their reported cases of hypogammaglobulinemia had splenic and lymph node enlargement. Though a diagnosis of giant follicular lymphoblastoma was suggested in all the three cases of Brem[6] mentioned above, in none could this diagnosis be substantiated. In one case, on autopsy, hyperplasia of the reticuloendothelial system was noted. No evidence for lymphoma was present. The authors concluded that the remarkable reticulum cell hyperplasia was secondary to hypogammaglobulinemia. Collins and Dudley[7] reported a case of hypogammaglobulinemia who had anemia, reticulocytosis, leukopenia, bone marrow erythroid hyperplasia and negative Coomb's test. These features suggested hypersplenism in their case. Young et al.[8] describe a case of hypogammaglobulinemia who had hepatosplenomegaly and lymphadenopathy. The lymph node biopsy revealed reticulum cell hyperplasia. Rosecan et al.[9] reported two cases with splenomegaly and hypogammaglobulinemia. One of them had granulocytopenia and this was believed to be due to hypersplenism. The spleen was irradiated in this case. Standaert and DeMoor[10] have reported an adult with hypogammaglobulinemia, hepatosplenomegaly, thrombocytopenia, leukopenia and hemolytic anemia. Ramos[11] described the case of a 77 year old man with hypogammaglobulinemia. X-ray evidence of thymoma was present for two years prior to admission. The thymoma was removed but the patient died postoperatively. No evidence of tumor was found on autopsy. The spleen weighed 730 Gm. Microscopic examination showed ill defined foci of extramedullary hematopoiesis. The pulp was markedly congested and contained scattered deposits of hemosiderin. Sinusoids were filled with a mixture of histiocytes and lymphocytes and littoral cells appeared prominent. Erythrophagocytosis and large bizarre reticulum cells were also found. It is clear that the splenomegaly was quite unrelated to the thymoma and that the anemia was due to hypersplenism. Martin et al.[12] have reported hypogammaglobulinemia in an adult who had hepatosplenomegaly and hemolytic anemia. Wechsler[13] records a case of acquired hypogammaglobulinemia with palpable spleen but no definite evi-

dence of hypersplenism. Barandun et al.[14] have reported a case of acquired hypogammaglobulinemia with hepatosplenomegaly, lymphadenopathy and leukopenia. Nonspecific granuloma and marked reticulum cell hyperplasia were present in the liver and the spleen. Brückel et al.[15] describe a case of acquired hypogammaglobulinemia, splenomegaly, anemia, leukopenia and thrombocytopenia. In all the cases mentioned above, no underlying cause has been found for the splenomegaly or reticulum cell hyperplasia, other than the hypogammaglobulinemia.

In the congenital type, cyclical neutropenia has been observed[16] which again may be a manifestation of hypersplenism.

At the time of the first report,[3] a distinct relationship between hypogammaglobulinemia, splenomegaly, hypersplenism and reticulum cell hyperplasia was not as obvious as it is now. It seems reasonable to presume that as a result of hypogammaglobulinemia and resultant repeated infection, reticulum cell hyperplasia results. This causes splenomegaly and hypersplenism. The hemolytic anemia has responded to splenectomy in our cases and the one reported by Rohn et al.[4] Often these cases have been incorrectly diagnosed as malignant lymphoma, as earlier pointed out. Arends et al.[17] reported a case of a middle aged woman who had absent gammaglobulin and was thought to have a malignant lymphoma, though the type of the lymphoma could not be determined. Although the absence of gamma globulin was ascribed to the lymphoma, Brem and Morton[6] believe that this case represents another instance of intense reticuloendothelial system hyperplasia in response to lack of gamma globulin and its consequences. Brem and Morton[6] had two patients in whom evidences of poor antibody response antedated the appearance of leukemias by many years in both instances. Such a globulin defect has not been found in the studies of serum proteins of many other cases of leukemia.[6] In the first reported case (L.L.)[3] which was also included in the groups reported by Good[16] and by Zinneman et al.,[18] nonspecific granulomas were seen in the liver, spleen and lymph node biopsies, in addition to generalized reticulum cell hyperplasia. A diagnosis of sarcoidosis was considered but was not acceptable on other grounds. The possibility that the granulomata cause the defect of hypogammaglobulinemia was mentioned[3] but at present this appears to be unlikely. Recently a case of hypogammaglobulinemia associated with tuberculosis has been reported.[19] The authors believe that tuberculosis was responsible for the production of hypogammaglobulinemia. Though the diagnosis of tuberculosis was not established bacteriologically, other evidences indicated this diagnosis. Yet, it is difficult to accept the view that a generalized tuberculous adenitis would affect but one particular function of the reticuloendothelial system, that concerned with the production of gamma globulin. Also, if this were true, a much more frequent association of acquired idiopathic hypogammaglobulinemia with tuberculosis might be anticipated. In reported cases of acquired idiopathic hypogammaglobulinemia where lymphatic system involvement has been observed, a careful scrutiny of the histories fail to indicate that the lymphatic disease really preceded the onset of the hypogammaglobulinemia. The mechanism of production of hypogammaglobulinemia remains unknown. It is quite conceivable that the primary fault lies in a disturbance in formation of

plasma cells[16] and that their absence and consequent hypogammaglobulinemia then serves as a stimulus to reticuloendothelial cell hyperplasia. Recently Wall et al.[21] have reported that the incidence of hypogammaglobulinemia is distinctly increased in diseases of the reticuloendothelial system (mainly neoplastic in type) as compared with other diseases. They noted that in some instances, hypogammaglobulinemia occurred long before the reticuloendothelial system disease was recognized. It would also be of interest to examine the gamma globulin in diseases such as the Felty's syndrome, the Wiseman-Doan syndrome, or the Letterer-Siwe disease.

Summary

Two cases of acquired idiopathic hypogammaglobulinemia associated with splenomegaly and hemolytic anemia due to hypersplenism have been reported. Splenomegaly and hypersplenism appears to be the result of reticulum cell hyperplasia caused by the lack of gamma globulin and resultant repeated infections. Both the cases had splenectomy with marked hematologic improvement.

A review of the literature indicates that this syndrome is relatively common, in comparison to the incidence of total number of acquired hypogammaglobulinemia that has been reported in the literature so far. It also seems very important to recognize it because of the obvious therapeutic implications. Serum gamma globulin level should be determined in cases with unexplained hepatosplenomegaly, hypersplenism and hemolytic anemia.

Summario in Interlingua

Es reportate duo casos de acquirite hypogammaglobulinemia idiopathic associate con splenomegalia e anemia hemolytic causate per hypersplenismo. Splenomegalia e hypersplenismo es apparentemente le resultato de hyperplasia reticulo-cellular causate per le manco de globulina gamma e le resultante frequentia de infectiones. In ambe casos, splenectomia resultava in un marcate melioration hematologic.

Un revista del litteratura indica que iste syndrome es relativemente commun in comparation con le incidentia total de hypogammaglobulinemia acquirite usque nunc reportate in le litteratura. Il pare importantissime recognoscer le syndrome correctemente a causa del obvie inferentias therapeutic. Le nivello seral de globulina gamma deberea esser determinate in casos con inexplicate hepato-splenomegalia, hypersplenismo, e anemia hemolytic.

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