HYPOGAMMAGLOBULINEMIA IN PYODERMA GANGRENOsum*

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Pyoderma gangrenosum is most commonly regarded as an infection in patients suffering from debility of unknown nature. A varying bacterial flora can be cultured from the skin ulcerations (4, 6, 7, 9), but no special agent seems characteristic of the infection. The disease runs a chronic intermittent course, as a rule attended by processes in other organs as well, particularly ulcerative colitis (2, 8, 9, 15, 20), but also genito-urinary infections, pleuritis, pericarditis (11, 21), peridental infection (4, 9), and nail affections (16). In a few cases the skin alone is affected (17). Our knowledge concerning factors predisposing to chronic infections of the organism is very deficient. Greater clarity seems to prevail regarding the liability to acute infections provoked by different agents. Bruton (3) in 1952 reported a case in which a pronounced liability to infections was accountable for by total agammaglobulinemia. This could be compensated for by a monthly addition of gamma globulin, which was then demonstrable in the serum. The result of Bruton's investigation highly supports the view that the hypogammaglobulinemia accompanying nephrosis likewise is responsible for the increased liability to infection demonstrated here (5, 14).

In a case of pyoderma gangrenosum it was therefore thought appropriate to determine the protein fractions in serum by electrophoretic analysis and attempt treatment with gamma globulin.

Such an attempt at treatment must a priori be regarded as difficult to evaluate owing to the capricious course of the disease, where early necrosis is followed by rapid formation of new epithelium (20). The sizes of the naked and the epithelium-covered plaques were therefore measured and photographed during the entire course. But, owing to the exudation, tenderness, and the irregularity of the ulcer surfaces, the results of the treatment could only be roughly assessed and indicated with intervals of 100 square centimeters.

CASE REPORT

A married man, aged 71, was admitted on Aug. 31, 1953. Apart from infectious children's diseases he had been well until the age of 41. From 1929 to 1933 he had had more than 14 episodes of eruptions of multiple or solitary ulcerations diagnosed as furunculosis and pyoderma vegetans. Only three of these had necessitated admission to hospital. In 1933 he was treated with Trypaflavine and milk injections during a 4 months' stay in a hospital. In 1935 and 1937 he was in a hospital for 5 months each time and treated with X-rays, Prontosil, and a vaccine prepared from Staphylococci, Proteus, B. pyocyaneus, and non-identified gram-negative rods isolated from the ulcerations. To judge from the sizes of the cicatrices and from photographs, the eruptions had been much smaller than the present one, which had begun 24 days before his admission with a rapidly increasing ulceration on the left side of the abdomen. On admission the ulceration was about 100 sq. cm., and it grew further, soon to be surrounded by a 2 cm. broad indurated red zone. The edge of the

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ulceration was slightly everted, undermined, and dark red. The deep-seated ulcer surface was covered by spongy necrotic tissue and very tender, slightly bleeding granulations exuding abundant mucopus. The clinical picture thus resembled Brunsting, Goeckerman, and O'Leary's original description (2).

**Biopsy** showed a deep-going acute inflammation of an unspecific character with abundant necrosis.

On admission the patient was normally developed, well-nourished, not suffering distress or feeling poorly, subfebrile.

**Clinical course.** The patient stayed in hospital for 116 days. Within this period about 5200 sq. cm. of skin underwent necrosis during two outbreaks of the disease (Fig. 1). The largest extension of ulcer surface without epithelium was 1200 and 2300 sq. cm. respectively. The course was subfebrile. The evening temperature only on rare occasions exceeded 38°C, and never 38.5°C, except after blood transfusion.

The general condition was marked by pain, insomnia, and tiredness; but the patient drank much fluid, and his appetite was good on a high-protein diet. No edema formation was observed. The weight fell steadily from 73 to 57.4 kg. On discharge, the large ulcerations had healed up, the temperature was normal, and there were no troubles, apart from a persisting tiredness. This condition was unchanged at the followup 26 days later.

**Analyses.** Various analyses were made daily or weekly during the whole course, but only those of importance in this connection will be reported here. Hemogram showed a moderate normochromic anemia and periodical leukocytosis. RBC count 3.3–3.8 mill/mm. Hgb. 71–82 per cent. Color index 1.01–1.10. ESR 145–78 mm/h. WBC count 5.8–8.2 thousand/mm, with 69–81 per cent neutrophiles, 2–4 per cent eosinophiles (113–322/mm). Fibrinogen 0.6. Coagulation 2–4 min. Bleeding 1.5–4 min.

Formolgel, Takata, Thymol, electrolytes, chlorides, bicarbonate, sugar, Coombs' test,
TABLE I

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<th>Date</th>
<th>Serum Protein, gm/100 ml</th>
<th>Albumin</th>
<th>Globulin</th>
<th>A/G Ratio</th>
<th>Relative Electrophoretic Concentrations Counts in Per Cent (Antweilers Microelectrophoretic Method)</th>
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cold agglutination titer failed to show any abnormality. So did urine chemistry and microscopy. BP 165/85. WR negative.

Gonadotropic hormones, estrogens, androgens, and 17-ketosteroids were normal.

Consultation with various departments, including ear, nose and throat, eye, medical and X-ray diagnostic, revealed no abnormal conditions, except a slight exocca and moderate arthropsis in the cervical region.

Especially it should be emphasized that no affection was demonstrated in the intestine, liver, or kidneys.

Serum proteins were determined by electrophoretic analysis according to Antweiler, total protein by precipitation with copper sulphate (Table 1). Moderate hypoproteinemia was observed with relative and absolute increase of the amount of globulin. This increase was due to the alpha-2 and beta globulins, whereas the gamma-globulin fraction was very low during the whole course, on several analyses even not traceable at all (Fig. 2). At the follow-up 26 days after his discharge (37 days after recovery) the albumin fraction, alpha-1 and alpha-2 had reached normal values, while the beta globulin still showed raised values and the gamma globulin still very low values.

Treatment with antibiotics. Before his admission the patient had been treated with penicillin. Culture revealed *Staphylococcus aureus*, resistant to penicillin.

Aureomycin, 1 g for 5 days, terramycin, 1 g for 10 days, and penicillin, 1.5 mill. daily for 14 days, destroyed the Staphylococci, but the culture was found to contain *Proteus*, sensitive only to streptomycin and chloromycetin. After 750 mg chloromycetin for 10 days the *Proteus* had disappeared, but now two strains of *B. pyocyaneus* were demonstrated, which were relatively or absolutely resistant to all antibiotics except streptomycin. After 2 g streptomycin for 4 days the *B. pyocyaneus* strains disappeared and were not later demonstrable. Treatment with antibiotics thus destroyed all the demonstrated bacteria. It had no influence on the progress of the necrosis, and no epithelium was formed. 3 weeks later staphylococci, proteus, and enterococci were found, and their normal sensitivity to antibiotics had recurred.

Treatment with gamma globulin. This treatment was tried during both outbreaks of the
Fig. 2. Electrophoresis curves during gangrene (88th day in Fig. 1) and 37th day after recovery.

disease. During the former 50 ml daily were given for 5 days and during the latter 50 ml daily for 3 days. The relation to the course of the disease appears from Fig. 1. The former course of treatment with 250 ml was given on the 51st to 54th days of existence of the first eruption, where 1200 sq. cm. were necrosed, while hardly any epithelium was formed. After 2 days of treatment excessive epithelium formation commenced, which continued for 24 days. The necrosis continued for 6 days, and on the eighth day a slight increase of the gamma fraction was demonstrated in the serum.

It was then intended to treat the anemia and the hypoproteinemia by blood transfusion. Blood from a donor of the same group B, Rh-pos., was used. After infusion of less than 5 ml the patient developed cold shivers, congestion, dyspnea, sweating, and lumbar pain. The transfusion was therefore discontinued. The temperature rose to 39.8° C, after which the symptoms subsided.

Erythrocytes were found in the urine, but no albuminuria, nor any influence on the urine flow. Careful revision undertaken by the Transfusion Department, the State Serum Institute, showed that the donor and the recipient belonged to the same main group and presented accordance as regards all the subgroups. No known antibody was demonstrated, and crossed compatibility test showed complete compatibility. Attempts at treatment with blood or albumin were not repeated.

Soon after the second outbreak 50 ml of gamma globulin daily were given again for 3 days, after negative scratch test as well as negative intracutaneous and subcutaneous tests. The effect on the epithelium formation was marked on the third day after the injection of gamma globulin, which this time was given on the fifth to seventh days after the onset of necrosis. The injections still had no definite effect on the necrosis, which continued until the 26th day after these. This time no rise of gamma globulin in the blood was demonstrated; on the contrary, this became untraceable. After the first outbreak the gamma globulin was given on the 51st to 54th days and after the second on the 5th to 7th days. In both cases epithelium began to be formed immediately after the injections.

DISCUSSION

Moderate hypoproteinemia with increase of the globulin fraction was ascertained in a patient suffering from pyoderma gangrenosum limited to the skin.
Several analyses revealed no gamma globulin, however, and the serum values remained very low during the whole course and 37 days after the healing. Injections of gamma globulin in large doses caused little or no rise of the serum level and had no definite effect on the course of the necrosis, but was twice followed by regeneration of epithelium on the ulcer surfaces. The hypoproteinemia and the hyperglobulinemia can be explained by exudation from the ulcer surfaces. The hypo- and agammaglobulinemia seems to be an independent phenomenon, Lever (12) having shown that the protein fractions by exudation from the skin are lost in the proportion in which they are present in serum, and Zeldis and Alling (22) that albumin regenerates at a very slow rate. Hypogammaglobulinemia in association with skin diseases does not seem to have been observed previously, in spite of frequent occurrence of hypoproteinemia (13). Only in cases of burns of the second and third degrees has a minor fall been noticed (18). It is remarkable that burns are particularly liable to infection with a mixed bacterial flora very similar to that in pyoderma gangrenosum. Agammaglobulinemia seems on the whole to be rare. In addition to Bruton's case only a very few constitutional cases are known. Hypo-gamma-globulinemia has been observed in nephrosis (5, 14) and malnutrition (18), factors that were not demonstrable in the present case. According to Tiselius and Kabat (19), most of the antibodies are present in the gamma-globulin fraction. Hypo-gamma-globulinemia might therefore explain the numerous mixed infections in pyoderma gangrenosum. As the gamma globulin level in serum presumably indicates the relation between production and consumption, the slight or failing rise of serum gamma globulin after injection of large amounts is explainable when we consider the relative sizes of the eruptions and the doses. The striking effect on the regeneration, compared with the slight effect on the progress of the necrosis can be accounted for by differences in permeability of the injected gamma globulin in the indurated active zone and in the large exudating surface. The conclusions that may be drawn from a single case are, however, naturally limited.

CONCLUSION

Two severe outbreaks of pyoderma gangrenosum were found to be associated with hypogammaglobulinemia, which was still considerable 37 days after the patient's recovery from the skin disease. Large doses of gamma globulin gave no or only a slight rise of this fraction in the serum and did not stop the progress of the necrosis. Marked regeneration of epithelium was observed after each injection of gamma globulin.

REFERENCES


