Hypogammaglobulin G, Hyperimmunoglobulin M, Intestinal Nodular Hyperplasia, and Thrombocytopenia

An Unusual Association

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Abnormalities of serum immunoglobulin levels are frequently associated with such haematological disorders as primary aregenerative anaemia, haemolytic anaemia, neutropenia, thrombocytopenia, and leukaemia (Good et al., 1962). Recently, Hermans et al. (1966) reported a group of patients with nodular intestinal lymphoid hyperplasia and hypo-\(\gamma\)-globulinaemia. We have now seen thrombocytopenia, immunoglobulin abnormalities (hypo-IgG with hyper-IgM), and intestinal lymphoid hyperplasia in a 2-year-old girl. This combination of features emphasizes the common origin of functional cells of the immunoglobulin production and haematopoietic systems, and provides interesting speculation on the relation between intestinal lymphoid tissue and immunity.

Case Report

A female child was admitted to University Hospitals for the first time at 5 months of age because of generalized lymphadenopathy, hepatosplenomegaly, and thrombocytopenia. Her mother had been exposed to rubella during the first months of pregnancy, but received \(\gamma\)-globulin and did not develop overt signs of infection. The neonatal period was unremarkable. At 3 months of age, hepatosplenomegaly was first noted. During the first hospital admission, Hb and white blood count were normal; Downey cells were seen in the peripheral smear. The platelet count was 52,000/cu. mm.; the bone-marrow showed no abnormalities. A throat culture, performed for isolation of rubella virus, was negative. Toxoplasma antibodies and heterophile agglutinins were absent. Blood VDRL test, negative. Examination of the urinary sediment for cytomegalic inclusion bodies was negative. She was discharged with a presumptive diagnosis of infectious mononucleosis.

Because of persisting hepatosplenomegaly, she was readmitted at the age of 7 months. The bone-marrow was again normal. A liver biopsy showed a slight excess of haemosiderin, but was otherwise normal. Diarrhoea was noted and tests for faecal occult blood were occasionally positive. She was discharged without a clear diagnosis.

In the interim, the diarrhoea persisted, seemingly aggravated by cow's milk and fruit juices. Grossly bloody stools were noted on some occasions. Hepatosplenomegaly persisted without change, while the platelet counts ranged from 70,000 to 150,000/cu.mm. Anaemia was never present.

These symptoms led to her third admission, at the age of 16 months. At this time, a coeliac appearance was noted. The liver edge extended to 4 cm. below the right costal margin and the spleen edge to 4 cm. below the left. Several ecchymoses were noted over trunk and lower extremities. Firm, mobile lymph nodes, about 2 cm. in diameter, were easily palpable in the neck and inguinal areas. Tonsils were present.

Hb was 11.1 g./100 ml.; WBC, total 8050/cu.mm.; with 4669 polymorphs, 2978 lymphocytes, 241 monocytes, and 161 eosinophils/cu.mm.; platelets 132,000/cu.mm.; ESR 3 mm./hr. Serum ornithine carbamyl transferase and prothrombin time were normal. Serum protein electrophoresis showed hypo-\(\gamma\)-globulinaemia. A xylose absorption test showed only 9% excretion 5 hours after the ingestion of the sugar (normal: 20% or more). Measurement of a 4-day faecal fat specimen showed 89% absorption. Stool cultures and examination for ova and parasites were negative; in particular, \textit{Giardia lamblia} was not found. Barium studies of the stomach and small intestine were normal, but a barium enema showed an irregular mucosal pattern with multiple defects (Fig. 1).

Proctoscopy showed a cobblestone appearance of the colonic mucosa. Biopsy showed a normal mucosal pattern overlying nodular lymphoid hyperplasia (Fig. 2).
An inguinal node biopsy taken at this time showed follicle formation with normal architecture and cellular distribution including plasma cells. Small bowel biopsy also showed lymphoid hyperplasia (Fig. 3).

Immunoglobulin levels determined by the radial diffusion method (Mancini et al., 1964) showed slightly low IgG and IgA, with raised IgM levels.* IgG was 333 mg./100 ml., IgA was 18·8 mg./100 ml., and IgM was 159 mg./100 ml. Levels determined in numerous relatives are shown in the Table. Though some of the values vary more than 1 SD from the mean of Stiehm and Fudenberg (1966) results, they fall within their normal ranges, except one sib whose IgA is slightly raised.

Rubella antibody titres were negative. The patient formed antibodies to Salmonella H antigens in a titre of 1:320. No agglutinins were formed to ‘O’ antigen. Active sensitization with 2,4-dinitrofluorobenzene was accomplished.

At 24 months of age, the patient had varicella. Dyspnoea preceded onset of the rash by one day. A chest x-ray showed a large unilateral pleural effusion and mild bilateral pneumonitis. Examination of the pleural exudate failed to reveal malignant cells. The immunoglobulin levels of the pleural fluid were: IgG 320 mg./100 ml., IgA 25 mg./100 ml., IgM 130·5 mg./100 ml. At this time serum levels were IgG

*Standards employed for these determinations utilize a pool of normal human serum obtained from 15 normal adults. The original values for immunoglobulins G, A, and M were determined by using normal immunoglobulins isolated in our laboratory and corroborated by Dr. E. R. Stiehm, University of Wisconsin.
Hypo-IgG, Hyper-IgM, with Thrombocytopenia

TABLE

Immunoglobulin Levels (mg./100 ml.) in Patient and Her Relatives

<table>
<thead>
<tr>
<th></th>
<th>Age (yr.)</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>14</td>
<td>333 (762 ± 209)*</td>
<td>18.8 (50 ± 24)</td>
<td>159 (58 ± 23)</td>
</tr>
<tr>
<td>Sister</td>
<td>2</td>
<td>470 (762 ± 209)</td>
<td>40 (50 ± 24)</td>
<td>306 (58 ± 23)</td>
</tr>
<tr>
<td>Brother</td>
<td>7</td>
<td>1040 (923 ± 256)</td>
<td>240 (124 ± 45)</td>
<td>62 (65 ± 25)</td>
</tr>
<tr>
<td>Sister</td>
<td>6</td>
<td>990 (923 ± 256)</td>
<td>138 (124 ± 45)</td>
<td>56 (65 ± 25)</td>
</tr>
<tr>
<td>Mother</td>
<td>4</td>
<td>880 (929 ± 228)</td>
<td>56 (93 ± 27)</td>
<td>68 (56 ± 18)</td>
</tr>
<tr>
<td>Father</td>
<td>38</td>
<td>1590 (1158 ± 305)</td>
<td>114 (200 ± 61)</td>
<td>154 (99 ± 27)</td>
</tr>
<tr>
<td>Maternal aunt</td>
<td>37</td>
<td>1190 (1158 ± 305)</td>
<td>195 (200 ± 61)</td>
<td>92 (99 ± 27)</td>
</tr>
<tr>
<td>Maternal grandfather</td>
<td>68</td>
<td>965 (1158 ± 305)</td>
<td>75 (200 ± 61)</td>
<td>56 (99 ± 27)</td>
</tr>
<tr>
<td>Maternal greatgrandmother</td>
<td>88</td>
<td>1365 (1158 ± 305)</td>
<td>113 (200 ± 61)</td>
<td>61 (99 ± 27)</td>
</tr>
</tbody>
</table>

*Mean ± 1 SD (Stiehm and Fudenberg, 1966).

470 mg./100 ml., IgA 40 mg./100 ml., and IgM 306 mg./100 ml. Because of her immunoglobulin abnormality, she was given a fresh plasma infusion from a donor who had recently recovered from varicella. The patient recovered from this illness without further incident. At no time in her history there has been an undue susceptibility to pyogenic infection.

An elder sister is said to have frequent bouts of respiratory infections. Another, aged 4, had an episode of non-thrombocytopenic purpura, abdominal pain, and melena when she was 2 years of age. Recovery from this event was uncomplicated, and she is now in excellent health. The family history is otherwise unremarkable.

Comment

The combination of thrombocytopenia, hypo-γ-globulinaemia, and intestinal lymphoid hyperplasia seems to represent a most unusual association. However, present concepts of the normal pathways of differentiation leading to immunological competence suggest a unifying hypothesis.

The intestinal follicular hyperplasia is a feature of particular interest, which bears upon two important concepts of modern immunology. One is the role of gut-associated lymphoid tissue in immunoglobulin production, and the other is the association of lymphoid hyperplasia or malignancy with hypo-γ-globulinaemia. Following the original observation by Glick, Chang, and Jaap (1956) that ablation of the bursa of Fabricius could lead to deficiency antibody function, Warner, Szenberg, and Burnet (1962), Mueller, Wolfe, and Meyer (1960), and Cooper, Peterson, and Good (1965) have further delineated the central role of this gut-associated organ in immunoglobulin production. From this concept of a central lymphoid organ which is an essential point in immunogenesis, one derives the corollary that disease of this tissue will lead to deficiency of the end-products. Cooper et al. (1966) have suggested Peyer's patch tissue as a mammalian bursal equivalent. Nodular lymphoid hyperplasia of the intestines in association with hypo-γ-globulinaemia may thus represent a clinical example of central lymphoid disease with associated end-product deficiency. Further examples exist in the well-described association of immunoglobulin deficiency in tumours of the thymus and of the plasma cells (multiple myeloma) (Peterson, Cooper, and Good, 1965). Since there was no generalized hypoproteinaemia, it seems unlikely that the gastrointestinal loss accounts for the hypo-γ-globulinaemia. Furthermore, though the patient no longer suffers from diarrhoea, the IgG levels remain low and the IGM shows further increases.

The frequent clinical association of haematological disorders and hypo-γ-globulinaemia supports the theory of a common source of haematological and immunologically concerned cells. Experimental evidence is provided in the observation that bone-marrow injections into irradiated mice (Micklem and Ford, 1960; Gesner and Gowans, 1962; Ford and Micklem, 1963) repopulate and restore not only the haemopoietic, but the lymphoid tissues as well. The recent restoration of lymphoid deficiency in a lymphopenic form of a-γ-globulinaemia is also relevant to this point (Gatti et al., 1968).

There is a superficial resemblance of this disease with the Wiskott-Aldrich syndrome. However, Wiskott-Aldrich patients show a much more profound susceptibility to infection, low rather than high serum IgM levels, and the outstanding serological defect, viz. absent isohaemagglutinins, which was not found in this case (Cooper et al., 1968).

The possibility remains that infection may have produced this syndrome. A role for infection in the aetiology of immunological deficiency syndromes is suggested by the recent demonstration of hypo-γ-globulinaemia and hypo-IgG with hyper-
IgM as a feature of the rubella syndrome (Soothill, Hayes, and Dudgeon, 1966). A possible explanation for our observations is that an intrauterine insult (e.g. infection, toxin) occurred at a time of common differentiation of the megakaryocyte and plasma cell precursors, and resulted in disordered platelet and immunoglobulin production. The hyperplasia may in turn represent an attempt of the ‘central lymphoid organ’ to compensate for a deficiency in immunoglobulin production. Since an increase in IgM can result from an intrauterine infection (Stiehm, Ammann, and Cherry, 1966), it is possible that the immunoglobulin pattern is simply due to a persistence of this influence. The magnitude of this reaction is unusual, however. Furthermore, the intestinal lymphoid hyperplasia would represent a most unusual response to an infectious agent.

It is of interest that there was no inordinate susceptibility to infection with pyogenic organisms such as is seen with classic α-γ-globulinaemia. While it is tempting to assume that the γ-globulin level, though diminished, was adequate for protection, since it exceeded the levels usually found in classic hypo-γ-globulinaemia, cases associated with low IgG and raised IgM are usually associated with frequent infections and sometimes a fatal outcome (Gitlin, Rosen, and Janeway, 1962; Hong et al., 1962). The patient’s immunological system, furthermore, seems functionally intact, since she could respond appropriately to administered antigens. Our experience in this case underlines the imperfect correlation of immunoglobulin levels with clinical symptomatology. Quantitative determinations should always be correlated with functional assays to assess accurately the adequacy of immunity. Nevertheless, it may also be that this patient is in an early stage of an ongoing disease process and that full-blown immunological deficiency with increased susceptibility to infection will appear in the future. Her unusual response to varicella infection could be suggestive of this course.

Summary

A case of hypo-IgG, hyper-IgM, nodular intestinal lymphoid hyperplasia, hepatosplenomegaly, and thrombocytopenia is described. The association of defects is consistent with the idea that the development of the lymphoid and haematological systems are intimately related, and probably dependent upon a common cell of origin, and suggests a relation of the intestinal lymphoid tissue to immunoglobulin production. No unusual susceptibility to pyogenic infection has as yet been noted in this patient.

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References


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