We describe a 27-year-old Dutch woman with the hyperimmunoglobulinemia D and periodic fever syndrome. During febrile attacks she occasionally presented with skin lesions on the distal parts of her upper and lower extremities, with the histologic picture of a leukocytoclastic vasculitis. Clear perivascular deposits of IgD and C3 were present in early lesional skin on immunofluorescence investigation. Circulating IgD immune complexes were demonstrated on several occasions, both during and in between clinical attacks. These findings are consistent with an IgD immune complex–mediated pathogenesis for the skin lesions. In 10 patients with other forms of immune complex vasculitis of the skin, minimal perivascular deposits of IgD were found in four cases. In these cases, however, IgD was never found as the solitary immunoglobulin class.

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Hyperimmunoglobulinemia D (hyper-IgD) and periodic fever syndrome is rare but well defined. Since the original description by Van der Meer and coworkers in 1984, similar cases have been reported by others, confirming the unique nosologic entity. The syndrome is characterized by recurrent attacks of high fever (≥39°C), for which no cause can be found, and a substantially elevated serum level of polyclonal IgD. The cause of this syndrome is still obscure, but it is possibly immune complex mediated.

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REPORT OF A CASE

A white woman, born in 1961, experienced febrile attacks almost every month during the first years of her life.
Accompanying symptoms were abdominal pain, diarrhea, and lymphadenopathy. Apart from an elevated erythrocyte sedimentation rate, leukocytosis, and occasional proteinuria and erythrocyturia with erythrocyte casts during febrile attacks, extensive investigations failed to reveal any underlying disorder. In 1980 the patient was first shown to have an elevated polyclonal serum IgD level (>7150 mg/L). During the last 7 years the attack rate has diminished. Also the character of the attacks has changed, abdominal pain and diarrhea no longer being prominent symptoms. Now, prodromal muscle weakness, light-headedness, and nasal congestions are followed by chills and a subsequent sharp rise of body temperature, which lasts for approximately 5 days. Often, cervical lymph nodes become tender. Painful erythematous macules and papules sometimes appear on the distal parts of her extremities and last for 5 to 10 days.

Recently, the patient again presented with painful erythematous papules around her ankles. Punch biopsy specimens were obtained from early lesional skin for histologic examination and direct immunofluorescence. Abnormal routine laboratory findings during the attack included an erythrocyte sedimentation rate of 55 mm/h, a leukocyte count of 10.4×10^9/L, and slight proteinuria and erythrocyturia with some erythrocyte casts. Normal findings included the hemoglobin level; differential cell count; liver and kidney function tests; CH50, C1q, C3, C4, and antinuclear antibody levels; antistreptolysin test; hepatitis serologic profile; and total IgE concentration.

Serum for IgD and for the determination of immune complexes was frozen immediately at −70°C. Serum IgD was determined by radial immunodiffusion. A C1q binding assay was performed as described elsewhere. IgD immune complexes were measured according to Hiemstra et al.19

Fig 1.—Biopsy specimen of erythematous papule showing fibrinoid changes of vessel walls and mixed neutrophilic and lymphocytic perivascular infiltrate with slight leukocytoclasia and a few extravasated erythrocytes (hematoxylin-eosin, original magnification X240).

Fig 2.—Perivascular deposits of IgD (left) and C3 (right) in granular staining pattern (immunofluorescence, original magnification X350).
Direct immunofluorescence was performed on serial cryostat sections with monospecific fluorescein isothiocyanate-conjugated antisera against C1q and C3 and against the heavy chains of human IgM, IgG, IgA, and IgD (Dakopatt, Copenhagen, Denmark). To validate these investigations, we investigated early lesional skin from 10 patients with histologically proved leukocytoclastic vasculitis for the presence of IgD.

RESULTS

The serum IgD level was 3110 mg/L (normal, <15 mg/L). The level of circulating IgD immune complexes was 1172 mg/L during the attack and ranging from 265 to 989 mg/L between the attacks. The C1q binding assay was 53 mgEq/L (normal, <10 mgEq/L) during the attack, whereas no C1q binding was found between attacks.

Routine histologic examination of the skin specimen from the patient revealed endothelial cell swelling, fibrinoid changes of vessel walls, and a mixed neutrophilic and lymphohcytic perivascular infiltrate with slight leukocytoclasia and a few extravasated erythrocytes (Fig 1). Direct immunofluorescence showed granular deposits of IgD and C3 in and around the vessel wall of upper dermal vessels (Fig 2). Other immunoglobulin deposits were not found.

Four of the 10 patients with proved leukocytoclastic vasculitis from other causes showed perivascular deposits of IgD (patients 2, 5, 8, and 9; Table 1). These deposits were minimal and seemed to coincide with the perivascular infiltrate. In all four cases, the deposits of IgD were found in combination with deposits of immunoglobulins of other classes.

COMMENT

In this article we describe a patient suffering from the hyper-IgD and periodic fever syndrome who showed perivascular deposits of IgD in early vasculitic skin lesions during an attack. No other immunoglobulin deposits were found in these lesions. This finding, together with the high concentration of serum IgD and IgD complexes, suggests an IgD immune complex nature of the attacks and of the skin lesions. However, it would not be correct to assume such a direct causal relationship without any restriction. Several investigators have shown that perivascular deposits of IgD are found in approximately 60% of the skin lesions of patients with vasculitis (Table 2). Our own limited study is in agreement with this. The meaning of these IgD deposits in terms of pathogenesis, however, is not at all clear. According to Parish, deposits of IgD may represent harmless deposits in preexisting lesions. Weidner does not comment on the presence of IgD, but regards the histotopical localization of the IgD a good measure of the age of a vasculitic lesion. An important point is that only one of the 50 patients who were included in these studies showed IgD as the single immunoglobulin class present.

Normally, IgD is a very minor component (less than 1%) of total serum immunoglobulins. Although at present much is known of its structure, physiologic localization, and behavior in the immune response, the biological function of both membrane-bound IgD and serum IgD still has to be determined.

Increased levels of serum IgD have been found in a number of apparently unrelated disorders and conditions, among which are diabetes mellitus; pregnancy; cigarette smoking; the hyper-IgE syndrome; ataxia telangiectasia; the acquired immunodeficiency syndrome and a variety of other immunodeficiency disorders; certain viral, fungal, and recurrent bacterial infections; and the hyper-IgD and periodic fever syndrome. Until it is clear exactly what causes the elevation of serum IgD, it seems to be legitimate to differentiate the hyper-IgD and periodic fever syndrome from other conditions associated with high levels of serum IgD by its distinct clinical picture.

The patient described herein had extremely high levels of serum IgD. It is possible that all kinds of antigens, such as agents that produce (subclinical) infections, and vaccines generate these IgD immune complexes and initiate clinical attacks.

Circulating IgD immune complexes were also detected in between attacks on several occasions. Since it was found in a recent study that IgD immune com-
plexes are also present in the serum of patients with increased levels of IgD who are not suffering from periodic fever, the question whether or not these complexes in patients with periodic fever reflect a pathologic state remains to be answered. According to the Clq binding assay, circulating immune complexes, possibly composed of IgG and/or IgM, were present concomitantly at the moment of the attack. An alternative explanation for this finding might be that some of the patients’ IgD immune complexes contain small amounts of Cl-binding IgG or IgM with similar specificity to antigen. These complexes may be detected in the Clq binding assay. However, only perivascular deposits of IgD and C3 and not of IgG, IgM, or Clq were found on direct immunofluorescence investigation. The perivascular deposits of C3 are compatible with the observation that aggregated IgD at high concentrations is able to activate complement via the alternative pathway.

We realize that we have only indirect evidence to substantiate the hypothesis that in the patient described, IgD immune complexes were crucial in the pathogenesis of the vasculitic lesions. If IgD immune complex vasculitis truly exists, it may well be confined to patients suffering from hyper-IgD and periodic fever.

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