

## Case report

# Raised serum immunoglobulin E in Wegener's granulomatosis

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**Conn, D. L., Gleich, G. J., DeRemee, R. A., and McDonald, T. J. (1976).** *Annals of the Rheumatic Diseases*, 35, 377-380. **Raised serum immunoglobulin E in Wegener's granulomatosis.** Five patients with Wegener's granulomatosis were found to have significantly raised serum immunoglobulin E (IgE) levels. The rise in IgE was not related to the extent of clinical involvement, was not part of a generalized serum immunoglobulin rise, and was not associated with eosinophilia. Raised serum IgE may be a clue to the pathogenesis of this disease.

Immunoglobulin E (IgE) is associated with skin sensitizing antibody activity and it is raised in the blood in patients with respiratory allergy, parasitic infection, atopic dermatitis, and occasionally other unusual types of chronic skin disease (Bennich and Johansson, 1971; Stone, Muller, and Gleich, 1973; Winkelmann and Gleich, 1973; O'Loughlin and others, 1976). We have recently observed a rise in the serum IgE in patients (5 of 7 patients studied) with Wegener's granulomatosis.

### Case reports

#### CASE 1

A 25-year-old male whose disease started in April, 1973 with a nasal discharge which persisted. In August, 1973 he developed arthralgias and an abnormal chest x-ray. A month later he became weak, fatigued, developed arthritis of the left knee, ankles, and metatarsophalangeal joints of the feet, skin lesions of the hands, legs, and feet, and mucosal ulcerations. He was started on prednisone 60 mg per day, and 10 days later a nasal biopsy showed a granulomatous vasculitis. He then developed tarry stools and an abdominal aortogram showed extra-vascular blood in the area of the terminal ileum. Abdominal exploration showed inflammatory ulcers of the terminal ileum and this portion of the ileum was resected revealing a necrotizing granuloma with vasculitis. Postoperatively he developed grand mal seizures but the disease was subsequently controlled with a combination of prednisone and cyclophosphamide.

Laboratory examination gave white blood count  $14.2 \times 10^9/l$  ( $14\ 200/mm^3$ ) with 76% neutrophils, 15% lymphocytes, 5% monocytes, and 1.5% eosinophils. Haemoglobin was 8 g/dl, erythrocyte sedimentation rate 86 mm in one hour, creatinine 212  $\mu\text{mol/l}$  (2.4 mg/100 ml). Urinalysis gave a grade III proteinuria and grade III haematuria with hyaline and red blood cell casts. 24-hour urine protein was 5.2 g. Serum albumin 19 g/l (1.9 g/100 ml) and gammaglobulins 3.0 g/l. Serum IgA 1.37 g/l, IgG 6.15 g/l, and IgM 1.21 g/l, and IgE was 3.131 ng/l. The total serum haemolytic complement was 43, rheumatoid factor 1:128, antinuclear antibody negative. Chest x-ray showed multiple soft infiltrates and large right perihilar mass. Sinus x-ray showed left frontal and bilateral maxillary sinus opacification.

#### CASE 2

A 32-year-old male whose disease began in January, 1973 with nasal congestion. In March, 1973 a nasal biopsy was performed showing necrotizing granuloma with vasculitis and he was started on prednisone elsewhere and was rapidly tapered. He then developed calf cramping, fever, necrotic lesions over the elbows, episcleritis, and ulcers in the mouth. He was then seen at the Mayo Clinic and started on prednisone 80 mg/day and cyclophosphamide 150 mg/day orally. One month later he developed grand mal seizures and was noted to have significant hypertension. Blood pressure was medically managed but difficult to control and the patient deteriorated with marked weight loss. He was later admitted with a *Proteus mirabilis* septicaemia which responded to treatment, was readmitted unconscious with significant

hypertension, blood pressure 210/120, and died in July 1973. Autopsy showed widespread healed vasculitis of the lungs, ileum, colon, and right parietal occipital area of the brain. There was widespread cytomegalovirus inclusion infection.

Laboratory examination before treatment in March gave a white blood count of  $17.4 \times 10^9/l$  ( $17\,400/mm^3$ ) with 83% neutrophils, 11% lymphocytes, 4.5% monocytes, and 1.5% eosinophils. Haemoglobin was 10.6 g/dl, erythrocyte sedimentation rate 95 mm in one hour, creatinine  $91 \mu\text{mol/l}$  (0.8 mg/100 ml), and urinalysis showed grade III proteinuria with grade III haematuria. Total serum haemolytic complement 89 units/l, rheumatoid factor negative, and antinuclear antibody negative. IgA was 5 g/l, IgG 11.3 g/l, IgM 0.42 mg/l, and IgE 1.181 ng/l.

#### CASE 3

A 75-year-old white female who presented in November, 1974 with a 7-week history of fever, chills, malaise, weakness, cough productive of yellow sputum, and epistaxis. Chest x-ray showed multiple rounded pulmonary infiltrates. Nasal biopsy showed focal necrotizing granulomas with vasculitis. A urinalysis gave a grade II proteinuria and red blood cells casts. Sedimentation rate was 112 mm/h (Westergren). Haemoglobin was 9.6 g/dl, and the white blood count was  $11.2 \times 10^9/l$  ( $11\,200/mm^3$ ) with 81% neutrophils, 9.5% lymphocytes, 4.5% monocytes, 4.5% eosinophils, and 0.5% basophils. Serum creatinine was  $80 \mu\text{mol/l}$  (0.9 mg/100 ml) on admission, rising to  $164 \mu\text{mol/l}$  (1.85 mg/100 ml) in a period of 3 weeks. Rheumatoid factor was negative. IgA was 1.5 g/l, IgM 0.64 g/l, IgG 7.2 g/l, and IgE was 1.364 ng/l. She was started on cyclophosphamide 100 mg daily. She died in January 1975 elsewhere and the precise cause of death is unknown.

#### CASE 4

A 30-year-old roofer who developed oedema of the face and legs in July, 1974 was admitted to a local hospital where he was found to have grade IV proteinuria and a serum creatinine of  $141 \mu\text{mol/l}$  (1.6 mg/100 ml). There were no casts in his urine. Diagnosis of nephrotic syndrome was made and he was treated with prednisone 40 mg/day plus spironolactone, which resulted in a weight loss of 14 pounds and loss of his oedema. Approximately 2 months later he developed pain and crusting in the nose which persisted in spite of continued prednisone therapy,

and he was seen at the Mayo Clinic in June, 1975. He had been on prednisone 5 mg/day for the previous 8 weeks in addition to spironolactone 25 mg/day. Biopsy of the nasal lesion showed necrotizing granuloma with vasculitis. Chest x-ray was normal. Urinalysis at that time gave grade II proteinuria with an occasional hyaline cast. Creatinine was  $80 \mu\text{mol/l}$  (0.9 mg/100 ml). IgA was 3.15 g/l, IgM 1.24 g/l, IgG 7.68 g/l, and the IgE was 1.555 ng/l. Erythrocyte sedimentation rate was 9 mm/h. Rheumatoid factor was negative. Haemoglobin was 17.6 g/dl, and white blood count was  $11.4 \times 10^9/l$  ( $11\,400/mm^3$ ) with 50% neutrophils, 17% bands, 25% lymphocytes, 5.5% monocytes, 1% eosinophils, and 1% basophils.

#### CASE 5

A 63-year-old male whose illness began with angio-neurotic oedema over the lips, cheeks, and tongue which was intermittent with free periods for as long as one month. This began about 2 years before onset of chronic nasal congestion. He experienced occasional epistaxis and intermittent fevers up to  $38.3^\circ\text{C}$  for months before being seen. Multiple biopsies taken from all nasal turbinates showed necrotizing granuloma with focal areas of vasculitis consistent with Wegener's granulomatosis. There was no evidence of disease in the lungs or the kidneys. The white blood cell count was  $9.2 \times 10^9/l$  ( $9\,200/mm^3$ ) with 71% neutrophils, 6% monocytes, 22.5% lymphocytes, and 0.5% eosinophils. Sedimentation rate was 62 mm/h (Westergren). Urinalysis was normal and serum creatinine was  $88.4 \mu\text{mol/l}$  (1.0 mg/100 ml). IgG was 17.5 g/l, IgM was 0.33 g/l, IgA was 3.65 g/l, and IgE was 1.925 ng/l.

Initial treatment was started with methylprednisolone 24 mg/day. Because of a poor symptomatic and objective response, he was switched to cyclophosphamide 50 mg twice a day in addition to prednisone 5 mg twice a day. Three years after starting therapy his nose was entirely healed. Cyclophosphamide was discontinued after 18 months because of dysuria which may have been due to cyclophosphamide. The prednisone was gradually tapered off.

#### Discussion

Serum IgG, IgM, and IgA levels have been reported in Wegener's granulomatosis and raised levels of IgA have been found (Fauci, Wolff, and Johnson, 1971; Fauci and Wolff, 1973). We found raised IgA

**Table I** *Laboratory abnormalities*

|              | White blood count<br>( $\times 10^9/l$ ) | Eosinophils<br>(%) | IgE*<br>(ng/l) | IgG†<br>(g/l) | IgA†<br>(g/l) | IgM†<br>(g/l) |
|--------------|--|--------------------|----------------|---------------|---------------|---------------|
| Case 1       | 14.2                                     | 1.5                | 3.131          | 6.15          | 1.37          | 1.21          |
| Case 2       | 17.4                                     | 1.5                | 1.181          | 11.3          | 5.0           | 0.42          |
| Case 3       | 11.2                                     | 4.5                | 1.364          | 7.2           | 1.5           | 0.64          |
| Case 4       | 11.4                                     | 1.0                | 1.555          | 7.68          | 3.15          | 1.24          |
| Case 5       | 9.2                                      | 0.5                | 1.925          | 17.5          | 3.65          | 1.33          |
| Normal range | 4.1-10.9                                 | 0-7.5              | 0.006-0.780    | 6.4-14.3      | 0.3-3.0       | 0.2-1.4       |

\* IgE method of analysis (Gleich, Averbeck, and Swedlund, 1971).

† IgG, IgA, and IgM method of analysis (Markowitz and Tschida, 1972).

Conversion: SI to traditional units—white blood count:  $1.0 \times 10^9/l \approx 1000/mm^3$ .

**Table II** *Clinical features*

| Case No. | Age (years) | Sex | Steroid prescribed | Affected areas    |      |       |      |       |
|----------|-------------|-----|--------------------|-------------------|------|-------|------|-------|
|          |             |     |                    | Upper respiratory | Lung | Renal | Skin | Joint |
| 1        | 25          | M   | 0                  | +                 | +    | +     | +    | +     |
| 2        | 31          | M   | +                  | +                 | +    | +     | +    | 0     |
| 3        | 75          | F   | 0                  | +                 | +    | +     | 0    | 0     |
| 4        | 30          | M   | +                  | +                 | 0    | +     | 0    | 0     |
| 5        | 63          | M   | 0                  | +                 | 0    | 0     | +    | 0     |

+ = present; 0 = absent.

levels in 3 of our 5 patients. The striking abnormality was raised serum IgE in these 5 patients (Table I). The raised IgE was not associated with a generalized rise in immunoglobulins or with eosinophilia.

There was no relationship of the raised IgE level to the extent of clinical involvement or concomitant treatment with corticosteroids (Table II). However, it is noteworthy that 2 of the patients had a nephrotic syndrome and 2 others had significant proteinuria. Also one patient had angioneurotic oedema of the face. Though evidence is lacking to incriminate IgE in the development of these lesions, the possibility does exist because in experimental acute immune complex disease specific antigen combines with IgE attached to the basophil which releases vasoactive amines which are responsible for the deposition of immune complexes and thus inflammation (Cochrane, 1971). Serum complement, determined in only 2 of the 5 cases, was normal. The possibility of an immune complex mediated mechanism of disease has not been adequately explored in Wegener's granulomatosis.

It is known that IgE-producing cells are located in the respiratory tract and gut (Tada and Ishizaka, 1970). It may be that raised serum IgE is a reflection of involvement of the respiratory tract, and these 5 patients all had involvement of the upper respiratory tract and 3 had involvement of the lower respiratory tract. On the other hand, there are other diseases such as chronic bronchitis affecting the respiratory tract which are not associated with raised IgE (G. J. Gleich and R. D. Miller, personal communications, 1976). Serum IgE is raised in patients with allergic rhinitis, allergic asthma, and atopic dermatitis, but our patients did not have such an allergic past history (Henderson and others, 1971).

Raised serum IgE may represent a specific

response to an inciting agent. It is part of the immune response in parasitic infections such as ascariasis or visceral larva migrans (Johansson, Bennich, and Berg, 1972) and has been raised in association with the acute phase of the pulmonary infiltration in bronchopulmonary aspergillosis (Patterson and others, 1973). Yet it is not raised in patients with pigeon breeders' disease or farmers' lung disease, suggesting that certain agents are capable of eliciting an IgE response, such as the aspergilli, and others are not. Another explanation for the raised IgE might be a defect in delayed hypersensitivity, and specifically an abnormality in the suppressor T cell function which regulates the IgE-producing cells and is reflected by raised serum IgE (Pierce, Peavy, and Tadakuma, 1975).

A case has been reported with oedema, allergic reactions, recurrent infections, and evidence of T lymphocyte deficiency with raised titre of rheumatoid factor serum IgE and IgA, and these serum abnormalities were thought to represent a lack of suppression of certain immunoglobulin-producing lymphocytes which occurred as a result of the T lymphocyte deficiency (Goldman and others, 1974). A similar phenomenon may operate in Wegener's granulomatosis although, using standard delayed skin tests and lymphocyte responsiveness to non-specific mitogens, a defect in delayed hypersensitivity has not been detected (Fauci and others, 1971).

Raised serum IgE may be a common abnormality in Wegener's granulomatosis, perhaps providing a clue to the pathogenesis and prompting future investigation, particularly into the role of infectious agents and of suppressor T cells in this disease. The presence of raised IgE may predispose the patient to certain clinical manifestations such as nephrotic syndrome.

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