

ease represents a hyperimmune reaction to an unknown aetiological agent such as a virus.

Our use of the "unqualified term necrotizing lymphadenitis" was criticised by Dr JM Woodruff of the Memorial Sloan-Kettering Cancer Center in a letter to the editor of the *American Journal of Surgical Pathology*.⁹ In response to this,¹⁰ I proposed the eponym "Kikuchi's disease," and I am pleased to note the positive reaction to this suggestion.

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Drs Ali and Horton reply as follows:

Clearly, our literature search was not as thorough as we had thought, and we stand admonished!

We stained our material using the naphthol-ASD-chloroacetate method, but were unable to identify any convincingly positive cells or debris. Feller *et al*¹ also used this technique but do not mention any positive findings.

The exact nature of the cells around the necrotic foci must remain in doubt. Professor Dorfman's study² suggested in the one case examined that the cells staining positively with T cell markers around the necrotic foci were cytotoxic/suppressor T cells, yet Feller *et al*¹ reported these cells to be of the helper/inducer type. Further, there are clearly some T cells that share differentiation antigens with histiocytes,³ and we found apparent transitional forms between immunoblasts and histiocytes ultrastructurally.⁴

The advantage of the eponymous term "Kikuchi's disease" is that it cannot be reduced to an acronym which would probably be the fate of necrotising lymphadenitis without granulocytic infiltration (NLGI).

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Classification of haemolytic uraemic syndrome

An increasing number of micro-organisms have been implicated in the pathogenesis of the haemolytic uraemic syndrome.¹ This syndrome is characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure; and seems to be a disorder of platelet and endothelial cell interaction.

In several cases verotoxin, an exotoxin cytopathic for monkey kidney cells (Vero), and neuraminidase, an enzyme chemically similar to verotoxin, have been identified. Of the stool isolates reported in haemolytic uraemic syndrome, various serotypes of *Escherichia coli*,² *Shigella dysenteriae serotype 1* (Shiga toxin),³ and *Campylobacter fetus jejuni*⁴ produce verotoxin and cause bloody diarrhoea, a typical prodromal symptom. So far, six cases of childhood haemolytic uraemic syndrome associated with *Streptococcus pneumoniae*, a neuraminidase producer, have been described.⁵ Case reports of different bacterial and viral isolates in haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura (an analogous adult syndrome) continue to flourish. There is often no attempt to identify the production of these important toxins, however, which may signify a common aetiology for the different micro-organisms implicated in the pathogenesis of haemolytic uraemic syndrome.

Incubation of sterile culture filtrates of verotoxin producing *E coli* with normal plasma will result in potent platelet aggregating activity.⁶ This is dependent on the platelet membrane glycoproteins IIB and IIIA. The premature release of unusually large factor VIII multimers, seen in haemolytic uraemic syndrome plasma,⁷ may also be an important mode of pathogenesis and result from damage to vascular endothelium by verotoxin. Neuraminidase, produced by a wide variety of micro-organisms, may have several pathogenic mechanisms. Direct platelet aggregating activity; deasialation of factor VIII to produce platelet aggregation; and exposure of the Thomson cryptantigen of platelets, red cells, and vascular endothelium have all been postulated.

Further work is necessary to define the mode of action of verotoxin and neuraminidase in producing this disorder of platelet and endothelial cell interaction. The pathogenic role of these exotoxins, however, is becoming increasingly obvious. Early detection of free faecal verotoxin and the identification of neuraminidase and verotoxin producing micro-organisms are essential steps in the diagnosis and management of haemolytic uraemic syndrome. Classifying haemolytic uraemic syndrome into verotoxin, neuraminidase, and non-exotoxin cases could provide valuable clinical information about this heterogeneous condition. The increased morbidity recently observed in childhood haemolytic uraemic syndrome⁸ and the difference in prognosis of epidemic and sporadic cases may be due

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to the action of these exotoxins. Such a classification may also provide a practical basis for the administration of specific antimicrobial chemotherapy, convalescent gamma globulin, and future development of an effective antitoxin. Greater awareness and better management of toxin mediated haemolytic uraemic syndrome should ultimately improve its prognosis.

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Do parathyroid and adrenal autoantibodies coexist?

The aetiology of idiopathic hypoparathyroidism remains unknown, although an autoimmune pathogenesis seems probable in some cases. Controversy exists over the prevalence of parathyroid autoantibodies in idiopathic hypoparathyroidism and in association with other autoimmune diseases.

Blizzard *et al*¹ found parathyroid specific antibodies in the sera of 46 of 74 (> 38%) of patients with idiopathic hypoparathyroidism, 25 of 93 (>26%) of patients with idiopathic Addison's disease, and in 6 of 245 (>6%) of controls, using an indirect immunofluorescence technique. These figures have remained unconfirmed.

Irvine and Scarth² studied sera from nine patients with idiopathic hypoparathyroidism and described an antibody to parathyroid oxyphil cells in one of these patients. Doniach and Bottazzo³ subsequently expressed the opinion that the oxyphil cell reactivity could be attributed to human specific mitochondrial antibodies. They further reported screening "normal, hyperplastic and adenomatous parathyroid glands with several hundred polyendocrine sera and hypoparathyroid cases." They identified only three sera that reacted specifically with parathyroid chief cells; one of which was obtained from a patient with idiopathic hypoparathyroidism.

We wished to obtain parathyroid autoantibody positive sera for the purpose of antigen characterisation. In view of the high incidence of parathyroid autoantibodies found in idiopathic Addison's disease, in Blizzard's series, and the known rarity of adrenal autoantibodies in the normal population (<0.1%)³ we determined to obtain adrenal autoantibody positive sera for parathyroid autoantibody assessment.

Methods

Twenty six adrenal autoantibody positive sera were obtained from six British immunology centres. Normal control sera were obtained from healthy volunteers. We also obtained sera from two patients with idiopathic hypoparathyroidism. All sera were stored at -20°C until assay.

A standard indirect immunofluorescence technique was used to determine the presence of autoantibodies.⁴ Parathyroid autoantibodies were assessed on unfixed 5µm cryostat sections of normal human parathyroid gland obtained at necropsy. All sera were applied to these sections, both undiluted and at a 1/5 (v/v) dilution. Five sera were additionally assessed on cryostat sections of a surgically resected parathyroid adenoma. Adrenal autoantibodies were confirmed and titrated on cryostat sections of normal human adrenal gland obtained at necropsy. Fluorescein isothiocyanate (FITC) conjugated sheep antihuman immunoglobulins G, A, and M (heavy and light chain) were applied as second antibody, and fluorescence was assessed using a

fluorescence microscope. Negative and positive controls were included in each batch of sections tested. Negative controls comprised replacement of test serum by buffer, replacement of test serum by normal human control serum, and replacement of both the test serum and FITC conjugate by buffer. A known autoantibody positive serum is normally titrated simultaneously with each batch of sections as a positive control. In the absence of a known parathyroid autoantibody positive serum an antinuclear antibody positive serum was substituted for this control on parathyroid sections. This was titrated and gave a satisfactory assessment of the performance of the conjugate.

Results

None of the 26 adrenal autoantibody positive sera and neither of the sera from the two patients with idiopathic hypoparathyroidism showed specific reaction with normal human parathyroid tissue. Similarly, the five adrenal autoantibody positive sera, which had been additionally assessed on a human parathyroid adenoma, failed to show any evidence of the presence of parathyroid autoantibodies. The Table shows the results of titration of the adrenal autoantibody positive samples by indirect immunofluorescence.

Discussion

If 26% of patients with idiopathic Addison's disease had parathyroid autoantibodies we would have expected to detect several patients with coexisting parathyroid and adrenal autoantibodies in our series. We found none, however, which suggests that such antibodies are rare. It may be argued that the differences between our findings and those of Blizzard¹ could be based on patient selection. It is likely, however, that many of our patients had adrenal disease. This opinion is supported by two factors. First, adrenal antibodies are rare in the general population (<0.1%) and when present are often associated with the disease. Second, many adrenal antibody positive patients who are

Table

Titre of adrenal autoantibodies	No of samples
1/160	1
1/80	1
1/40	4
1/20	5
1/10	10
1/5	1
Insufficient sample	4