with conventional radiotherapy.[19] Only four of our 19 patients, however, were younger than 20 years of age when irradiated.

The development of Nelson's syndrome is the most serious complication of bilateral adrenalectomy, and two recent series reported incidences of 29% and 28%.[25 26] Though conventional radiotherapy does not prevent the development of Nelson's syndrome,[27] it does seem to reduce its incidence.[28] Whether low dose radiation treatment will exert a similar beneficial effect in patients who subsequently require adrenalectomy is not known. Five of our patients had an adrenalectomy and were followed up for two to eight years with no evidence of Nelson's syndrome.

In conclusion, we recommend that patients with Cushing's disease be offered initial treatment with low dose radiation treatment, especially in centres where neurosurgical skill in microadenomectomy is not readily available. Those patients who do not have remission of their disease by one year after radiotherapy should be considered for bilateral adrenalectomy. We believe that by this approach at least one third of patients with Cushing's disease have a chance of cure with a relatively simple and non-invasive treatment, which in our experience does not have any complications.

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Lymphadenopathy and selective IgA deficiency

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Abstract

Four men presented with unexplained lymphadenopathy. Three had a history of recurrent respiratory infections for several years, and two had lymph node or hepatic granulomas. None was noted to have symptoms of immunodeficiency at the time of presentation.

In one patient routine direct immunofluorescence study failed to detect IgA, and immunological investigations were therefore conducted in the rest. In all patients the findings were similar and characterised by a severe deficiency of IgA.

In the absence of a more serious cause selective IgA deficiency may be enough to explain "idiopathic" lymphadenopathy.

Introduction

Lymphadenopathy is a common clinical problem with a multitude of causes including, on rare occasions, immunodeficiency syndromes. Although it is a recognised feature of common variable hypogammaglobulinaemia in a minority of patients,[1] lymphadenopathy has not been associated with selective IgA deficiency. The four cases reported here suggest that it may not only be associated with IgA deficiency but may be a presenting feature.

Case histories

CASE 1

A 29 year old man had been investigated on three occasions over five years because of recurrent axillary lymphadenopathy and nocturnal sweating. On each occasion lymph node biopsy had shown follicular hyperplasia and granulomas without evidence of mycobacterial or fungal infection. Thrombocytopenia had also been present, which

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Results of immunological studies (normal values given in parentheses)

Case No	Serum immunoglobulins (g/l)			IgG subclasses (g/l)				IgG tetanus toxoid antibody (mg/l) (>4)	Auto-antibodies
	IgG (5·0-16·0)	IgM (0·5-1·5)	IgA (1·0-3·0)	1 (3·2-10·2)	2 (1·2-6·6)	3 (0·16-1·94)	4 (<0·03-1·33)		
1	10·1	1·2	<0·05	7·3	0·5	1·8	<0·03	<1	0
2	8·8	1·9	0·06	7·6	0·8	1·4	<0·03	2	0
3	11·0	1·3	0·06	10·9	0·7	0·7	0·12	614	0
4	16·1	3·2	<0·05	ND	ND	ND	ND	1/640*	0

ND = Not done.
* Measured by passive haemagglutination (normal > 1/160).

persisted, with platelet counts between 30 and 140×10^9/l. Bone marrow biopsy showed numerous megakaryocytes. Serum platelet antibodies were not detected. Liver and spleen were not enlarged. Repeat Kveim tests, Mantoux tests, and routine serological investigations for lymphadenopathy and fever had given negative results. A probable diagnosis of sarcoidosis had been made but he had shown no other clinical or laboratory features. In addition, there had been recurrent and persistent episodes of respiratory tract infection with bronchitis. *Haemophilus influenzae* had been cultured from his sputum during some of these episodes. Chest radiographs showed chronic shadowing in the lingula, thought to be postinfective. Appearances on bronchoscopy were normal.

CASE 2

A 27 year old man was investigated because of lymphadenopathy, enlarged liver and spleen, and weight loss. A lymphangiogram was non-contributory. Splenectomy and abdominal lymph node biopsy were performed at laparotomy, and histological examination of each showed follicular hyperplasia. A severe postoperative chest infection brought to light a history of recurrent respiratory tract infections for several years. During this and subsequent episodes of infection there was severe bronchitis with the isolation of *H influenzae* from sputum on several occasions.

Because of recurrent abdominal pain and vomiting a second laparotomy was performed one year later. Liver biopsy showed multiple non-caseating granulomas of undetermined cause. Subsequently he developed pernicious anaemia with achlorhydria and hypothyroidism with a goitre. Serum vitamin B_{12} concentration was 10 ng/l (normal 170-900 ng/l) and a Schilling test result was diagnostic of pernicious anaemia. Plasma thyroxine concentration was 57 nmol/l (4·4 μg/100 ml; normal 60-145 nmol/l (4·7-11·3 μg/100 ml)) with a high basal thyroid stimulating hormone concentration of 14·5 mIU/l (normal 1·1-7·5 mIU/l), which rose to 48 mIU/l after an injection of thyrotrophin releasing hormone. Both conditions required replacement therapy.

CASE 3

A 23 year old man had suffered from recurrent upper respiratory tract infections since his early teens. When aged 18 he was investigated for recurrent cervical lymphadenopathy and fever. Routine investigations failed to disclose a cause and lymph node biopsy showed reactive changes only. There was eventual spontaneous resolution. For two years before referral the respiratory tract infections had become more severe with recurrent episodes of bronchitis, often associated with haemoptysis. Chest radiographs showed bilateral basal shadowing. Although sputum was always purulent during infections, pathogenic bacteria had not been cultured.

CASE 4

A 45 year old man was investigated because of anorexia, weight loss, and generalised lymphadenopathy. He had a history of recurrent pityriasis versicolor but was otherwise asymptomatic. Routine investigations showed no cause for the lymphadenopathy. Lymph node biopsy showed reactive changes only, but on routine direct immunofluorescence IgA plasma cells were not detected.

None of the patients were taking drugs that might have caused the IgA deficiency.

Methods and results

The table gives the results of the immunological investigations. Serum immunoglobulins were measured by automated immunoprecipitation and, in addition, by radial immunodiffusion using rabbit anticolostral IgA (Dako, Denmark) for IgA. Measurement of immunoglobulins on several occasions in all patients showed consistent findings. Serum IgG subclasses were measured by radial immunodiffusion using monoclonal antisera[2] and IgG tetanus toxoid antibody by an indirect enzyme linked immunosorbent assay[3] or passive haemagglutination. All sera were examined by conventional techniques for autoantibodies to nuclei, smooth muscle, mitochondria, gastric parietal cells, thyroid microsomes, and thyroglobulin.

Comment

Although lymphadenopathy may be a feature of several immunodeficiency diseases, it is not a recognised complication of selective IgA deficiency. Indeed, many patients with selective IgA deficiency do not have symptoms, although there is an association with autoimmune diseases, allergic diseases, and recurrent respiratory tract infections, which are often minor but sometimes severe.[4] Three of the present four patients had severe respiratory tract infections associated with low IgG tetanus toxoid antibody responses or low serum concentrations of the IgG2 and IgG4 subclasses, or both, suggesting that they were different from most patients with IgA deficiency. Interestingly, two of the patients also had lymph node or hepatic granulomas. Granulomatous disease, usually of the lung but also of the liver, may occur in patients with common variable hypogammaglobulinaemia.[1 5]

Unlike other immunodeficiency syndromes, in which lymphadenopathy is part of a clinical picture dominated by recurrent infections often associated with other complications, the symptoms of immunodeficiency in these four patients were either minor or overlooked at the time of presentation with lymphadenopathy. In three of the four, however, severe infections were eventually a major feature. Although more serious causes must be excluded, the presence of selective IgA deficiency—particularly with symptomatic immunodeficiency—may be enough to explain "idiopathic" lymphadenopathy.

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