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Sensitisation to human insulin

With the introduction and widespread use of highly purified animal insulins, allergy to insulin has become rare. A few patients still develop allergic reactions to these "clean" insulins, however, and it was thought that recently available human insulins would provide them with an alternative. Unfortunately, generalised allergic reactions have occurred to both semisynthetic human insulin^{1,2} and human insulin of recombinant deoxyribonucleic acid (DNA) origin.³ We report a case suggesting that sensitisation to bovine or porcine insulin could result in crossreactive hypersensitivity to human insulin.

Case report

A 75 year old man with cirrhosis of the liver was diagnosed as having type II diabetes mellitus. He was put on a low carbohydrate diet but was later prescribed a mixture of highly purified bovine and porcine insulins (Lentard, Novo) to improve control. He administered the insulin intermittently and a few months later began to notice immediate local reactions. Soon afterwards, one injection was quickly followed by a severe urticariform reaction. An intradermal test performed 24 hours later with 4 U purified porcine insulin again resulted in immediate urticaria. We planned to transfer the patient to human insulin of recombinant DNA origin (Humulin, Lilly) but first performed double blind intradermal and skin prick tests with insulins, diluting fluids, zinc, and saline solution. Purified porcine insulin 10⁻⁶ U and both purified bovine and human recombinant DNA insulins 10⁻⁴ U produced positive reactions at 15 minutes, but there were no delayed reactions. A controlled passive cutaneous (Prausnitz-Küstner) test on a selected human volunteer elicited a strong reaction to porcine insulin 10⁻³ U and a weaker one to bovine and human insulins 10⁻² U.

Specific IgE antibodies to bovine and porcine insulin were measured by means of a radioallergosorbent test, which gave highly positive results (score 3) in both cases. As a radioallergosorbent test for human insulin is not yet commercially available we used a polystyrene tube radioimmunoassay (which is known to be less sensitive) for human insulin, and obtained a negative result. Nevertheless total specific binding of human insulin to the patient's plasma was 72% as measured by radioimmunoassay, with a serum concentration of more than 0.305 nmol/l, proving that high affinity IgG antibodies to human insulin were also present. Furthermore, specific histamine release from basophils was elicited by an automated method, either by bovine (25% of total histamine), porcine (12%), or human (23%) insulins. The lymphoblastic transformation test which was performed only to porcine and bovine insulins also gave a highly positive result (index 3.35 to porcine and 4.22 to bovine insulins). A diagnosis of atopy was excluded as the patient had no history of allergy or specific IgE to common environmental allergens (including pollen, moulds, and foods) and the total serum IgE concentration was 50 U/ml.

Comment

Altman² and Blandford⁴ have suggested the possibility of animal insulins inducing hypersensitivity to human insulins in the few patients with clinical allergy to human insulins, and we have described such

sensitisation. Our patient developed severe clinical allergy to a mixture of porcine and bovine insulins but had not received human insulin. Both the clinical and laboratory data showed antibodies to human insulin of both IgE and IgG classes, thus confirming that sensitisation to animal insulins may lead to human insulin hypersensitivity. This may be because IgE antibodies produced by insulins of animal origin "recognise" human insulin by cross reactivity.^{4,5} Although differences between amino acid sequences do exist, their effects on tertiary or quaternary structures of insulins would be minor. On the other hand, the sensitisation process may be enhanced by the habitual use of subcutaneous injections, known to be highly immunogenic, in exogenous insulin treatment.

These facts suggest that any change from animal to human insulins in patients known to be allergic to insulin must be made with great precaution. There are no reports to date of generalised allergic reactions in patients starting treatment with human insulins. We therefore consider that treatment with human insulin should be considered initially in patients with atopy or allergy to drugs.

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Pneumoperitoneum without faecal peritonitis in a patient with pseudomembranous colitis

We present a unique case of pneumoperitoneum without faecal peritonitis in a patient with pseudomembranous colitis.

Case report

A 58 year old woman with severe rheumatoid arthritis underwent surgery for total replacement of the right hip. Prophylactic cephadrine 500 mg three times daily was given until the sixth day after operation, when diarrhoea developed which failed to respond to treatment with kaolin and diphenoxylate hydrochloride (Lomotil). On the 14th day she had 18 bouts of diarrhoea and had a temperature of 38°C. Her abdomen was distended and tympanitic, but not tender. Her white cell count was 10.3 × 10⁹/l. Sigmoidoscopy showed a pseudomembrane and a small amount of blood. Histological examination of the rectal mucosa showed features consistent with pseudomembranous colitis. *Clostridium difficile* toxin was isolated, and vancomycin 500 mg four times daily was started.

She continued to have diarrhoea and on the 22nd day complained of a bloated abdomen. Her abdomen was distended and tympanitic, but soft and non-tender. Her temperature was 37°C and white cell count 12.5 × 10⁹/l. A chest radiograph showed a large amount of free gas under the diaphragm.

At operation the bowel was seen to be intact with no macroscopic perforation, but on manipulation numerous pinhole perforations appeared in the diaphanous wall of the descending colon. We performed a left hemicolectomy and fashioned the bowel ends as a double barrelled colostomy in the left iliac fossa. She made an excellent recovery and was discharged for orthopaedic rehabilitation after nine days. Histological examination of the

colon showed active inflammation with pronounced mucosal fissuring ulceration that extended through the bowel wall. The appearances were consistent with the diagnosis of pseudomembranous colitis.

Comment

Pseudomembranous colitis is a well recognised complication of treatment with oral antibiotics and causes severe and persistent diarrhoea. The diagnosis is confirmed by sigmoidoscopy and rectal biopsy and by isolation of the *Clostridium difficile* organism or toxin. Treatment consists of maintaining fluid balance and administering oral vancomycin 500 mg four times daily. In cases which fail to respond to these measures, diarrhoea may persist and toxic megacolon or septicaemia may develop. In these circumstances surgical resection of the colon may be necessary.¹⁻³ There have been only two cases reported of perforation of the colon secondary to pseudomembranous colitis.^{4,5} Both patients were extremely ill and had obvious signs of generalised peritonitis.

There has been no previous report of a patient with pseudomembranous colitis developing pneumoperitoneum without evidence of generalised peritonitis, systemic toxicity, or frank perforation. We assume that in our patient the very thin wall of the inflamed colon allowed the transudation of gas but not the escape of liquid faeces. In the absence of faecal contamination of the peritoneal cavity signs of peritonitis did not develop.

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Carcinomatous meningitis diagnosed with monoclonal antibodies

The diagnosis of neoplastic meningitis is confirmed by the demonstration of malignant cells in the cerebrospinal fluid, but such cells can be difficult to identify in conventional cytological preparations. By using monoclonal antibodies as markers for tumour cells in cerebrospinal fluid we successfully diagnosed carcinomatous meningitis in a patient in whom previous investigations had given negative results.

Case report

A 57 year old woman presented with a six month history of anorexia and weight loss followed by a deep vein thrombosis and bilateral pleural effusions that were drained but did not show malignant cells on cytological examination. A computed tomogram of the body obtained at that time was considered to be normal. She subsequently became confused and ataxic, at which time a computed tomogram of the brain showed hydrocephalus. An initial lumbar puncture showed clear cerebrospinal fluid at a pressure of 37 cm H₂O containing 10⁶/l white cells (1/mm³), a normal protein concentration of 0.35 g/l, but a low glucose concentration of 0.5 mmol/l (9 mg/100 ml) (blood glucose concentration 8.2 mmol/l (148 mg/100 ml)). No malignant cells were seen on cytological examination. A second specimen of cerebrospinal fluid gave almost identical results. By this time physical examination showed a possible pelvic mass, and neoplastic meningitis was diagnosed. She was admitted to the department of neurosurgery at Frenchay Hospital, Bristol, where a third lumbar puncture was performed.

Cytological examination showed a scanty deposit of degenerate cells, which were interpreted as being reactive rather than neoplastic. Monoclonal antibody testing was carried out on this sample using indirect immunofluorescence on unfixed cytospin preparations. We used a panel of antibodies comprising markers for epithelial cytokeratin, neuroectodermal cells, leucocytes, and carcinoembryonic antigen. The table shows the results. Immunostaining with LE61 showed scattered cells of epithelial origin, some of which were vacuolated. These cells contained carcinoembryonic antigen as shown by L11/285/14. All other cells were confirmed as being leucocytes, mostly T lymphocytes. No cells of neuroectodermal origin were found.

These findings led us to suggest several further investigations including gastroscopy, which resulted in a diagnosis of gastric carcinoma. When she ultimately died necropsy showed linitis plastica with ovarian metastasis and widespread meningeal infiltration.

Results of immunofluorescence tests with a panel of monoclonal antibodies

Antibody	Reference	Antigen	Result
LE61	1	Epithelial cytokeratin	Positive
L11/285/14	Unpublished	Carcinoembryonic antigen	Positive
2D1	2	Panleucocyte	Positive
UCHT1	3	T cell membrane	Positive
UJ13A	4	Pan-neuroectodermal	Negative

Comment

The difficulties of making a swift and accurate diagnosis of neoplastic meningitis are shown by this case, in which repeated cytological examination of the cerebrospinal fluid gave negative results. The use of appropriate monoclonal antibodies in a straightforward immunofluorescence test resulted in the confident identification of carcinoma cells, which were also shown to contain carcinoembryonic antigen. Cytological appearances of the cerebrospinal fluid generally deteriorate rapidly, but use of the marker LE61 for cytokeratin confers the advantage that the cerebrospinal fluid can be tested at leisure or after transport to a specialised laboratory as the antigen remains stable for at least three days (personal observations).

Monoclonal antibodies that recognise tissue differentiation antigens and tumour associated antigens appear to be ideal markers for identifying cells in any cytological preparation but have only recently been used in the cytological examination of cerebrospinal fluid.⁵ Our experience with this patient and others examined in the past two years suggests that immunofluorescence testing with monoclonal antibodies will greatly increase diagnostic accuracy in neoplastic meningitis, with resulting impact in clinical management.

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