Hepatitis B virus markers in patients with acute hepatitis B

<table>
<thead>
<tr>
<th>Months after onset</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgM</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

1. AAg = hepatitis B surface antigen (Blood Products Laboratories, Elstree).
2. eAg, cAg, anti-HBc IgM = hepatitis B "e" antigen, "c" antibody, or IgM class core antibody (Wellcome Diagnostics, Darfford).

appearance of anti-HBc IgM antibody. Larger studies indeed confirm that "e" antigen to "e" antibody seroconversion occurs one to two months after the onset of symptoms, when acute HBV infection resolves; the disappearance of anti-HBc IgM antibody (even when assayed in a 1:1000 serum dilution) occurs only three to four months after this event.1-Assay of "e" antigen and "e" antibody responses therefore permits earlier confirmation of the diagnosis of acute HBV infection than does assay of anti-HBc: IgM antibody responses. Assay of anti-HBc: IgM antibody therefore has a major role in the diagnosis of acute hepatitis B only when hepatitis B surface antigen is absent from the serum.1- In surface antigen positive cases the diagnosis is best made by detection of "e" antigen to "e" antibody seroconversion in serial serum specimens.

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Pulmonary aspergillosis in patients with leukaemia

We read with interest the paper by Boon et al concerning the serious problem of cerebral aspergillosis in liver transplant recipients.1- Our recent experience in patients receiving chemotherapy for haematological malignancy indicates a similarly extensive problem in this patient group.

Since November 1987 we have treated 81 patients with intensive inpatient chemotherapy for acute leukaemia or lymphoma. Twenty eight subsequently underwent autologous or allogeneic bone marrow transplantation. All patients received prophylactic, oral, non-absorbable antifungal treatment but none received systemic antifungal agents prophylactically. All bone marrow transplant recipients, but not those receiving standard chemotherapy, were nursed in sterile isolation. There were 15 episodes of aspergillosis infection confirmed by culture during this period, predominantly due to Aspergillus fumigatus, indicating an infection rate of 19.1%. Fourteen patients had primary pulmonary infection and one an isolated cerebral infection; four patients with pulmonary infection also had aspergillus generally disseminated to other sites. All patients contracted aspergillosis infection during chemotherapy for leukaemia or lymphoma; interestingly, no autologous or allogeneic bone marrow recipients were shown to be infected, indicating a protective effect of sterile isolation. Infection did not correlate with age or specific disease type. Aspergillosis infection was diagnosed during life in 10 patients, six by bronchoalveolar lavage, three by histological examination of excised lung, and one by antigen titre. Aspergillosis was present in the remaining five patients at necropsy. All but one patient were treated with intravenous antifungal treatment (ampoterixin B 1 mg/kg daily), identified by clinically suspected fungal infection during life. Despite this, seven (47%) patients died of aspergillosis infection. A seasonal variation in incidence of aspergillosis infection is suggested by our data in that only one episode was diagnosed in the months May to September. Any temporal pattern, however, is more likely to be related to regular and extensive hospital building works which have been well documented as a source of outbreaks of aspergillosis infection in bone marrow transplant recipients.1-2

Aspergillosis infection is well known to be a problem in patients receiving chemotherapy for haematological malignancy, and our experience supports this made clear by Boon et al regarding aspergillosis in immunocompromised patients. In view of the high mortality, despite treatment, it is accepted that an aggressive approach to treatment is required. The generally poor diagnostic yield from fibroptic bronchoalveolar lavage1 makes treatment on clinical suspicion alone necessary.

POTENTIAL BENEFIT OF 1,25-DIHYDOXYCHOLECALCIFEROL IN HYPOMAGNESASIA INDUCED BY CYCLOSPORIN

The association between cyclosporin neurotoxicity and hypomagnesaemia in allogeneic bone marrow recipients was reported in 1984.1- Despite lowered serum magnesium concentrations, urinary excretion of magnesium remains inappropriately high, an effect assumed to be due to a defect in renal tubular reabsorption of magnesium as a result of taking cyclosporin. Treatment with oral or parenteral magnesium is usually successful, but large doses of oral magnesium salts are often poorly tolerated because of diarrhoea. Reduction of renal magnesium excretion using amiloride may be helpful, but the combination of this drug with cyclosporin may give rise to hyperkalaemia. In this report we describe a patient with persistent symptomatic hypomagnesaemia after treatment with cyclosporin A who was given 1,25-dihydroxycholecalciferol with subsequent correction of the serum magnesium concentration.

Case report
A 44 year old woman with acute myelomonocytic (M4) leukaemia in second remission received an allogeneic bone marrow transplant and prophylaxis with cyclosporin A. Myelo-versus-host disease ensued with typical skin manifestations and diarrhoea. High dose prednisolone was given and cyclosporin A continued. Paraesthesias and muscle cramps developed, and both the serum magnesium and calcium were subnormal at 0.33 mmol/l and 1.3 mmol/l, respectively, the serum albumin concentration being 35 g/l. Chvostek's and Trousseau's signs were present, and intravenous magnesium and calcium replacement was begun. Subsequently oral magnesium was given in the form of Maalox, but doses above 20 mmol/day worsened the diarrhoea. Despite several infusions of magnesium (25–50 mmol/day), the serum magnesium concentration repeatedly fell below the reference range and paraesthesias recurred. Urinary magnesium excretion remained inappropriately high (figure), and amiloride, 5 mg twice a day, was given but had to be withdrawn because of hyperkalaemia. The serum concentration of 1,25 dihydroxycholecalciferol was subnormal at 10 pg/ml (reference range 18–66 pg/ml), and in an attempt to increase gastrointestinal absorption, and possibly renal tubular reabsorption of magnesium, 1,25-dihydroxycholecalciferol 250 ng/day was begun. The serum magn-
Parathyroid hormone related peptide in ovarian carcinoma

Hypercalcemia is one of the most common paraneoplastic syndromes encountered clinically, being associated with an estimated 10–20% of all solid tumours. Many factors contribute to this syndrome of humoral hypercalcemia of malignancy (HHM), including cytokines and prostaglandins of the E series. Recently, a peptide structurally and immunologically distinct from parathyroid hormone (PTH), but with parathyroid hormone bioactivity, has been implicated in the pathogenesis of HHM and has been termed parathyroid hormone related peptide or PTHrP.1

Hypercalcemia is associated with ovarian carcinoma frequently enough for the ovary not to be regarded as a primary tumour site in women presenting with clinically unexplained hypercalcemia.2 We therefore felt it would be of interest to examine a number of ovarian carcinomas for the presence of PTHrP.

Immunocytochemistry was performed using an antibody raised against the first 34 amino acids of PTHrP (kindly donated by Drs GV Segré and H Jüppner, Boston, Massachusetts, USA) and standard indirect immunocytochemical techniques. Two cases of ovarian carcinoma associated with hypercalcemia (one small cell and one non-small cell type, supplied by Dr GR Dickerson, Boston) were found to contain PTHrP. PTHrP was present throughout the cytoplasm of the tumour cells but was absent from inflammatory and stromal cells and areas of tumour necrosis. The immunoreactivity was completely abolished when the antibody was pre-incubated with PTHrP (1–34) overnight. Two cases of serous cystadenocarcinoma and two cases of mucinous cystadenocarcinoma of the ovary (from patients who were normocalcaemic) were found to be negative for PTHrP.

Normal adult ovary does not produce PTHrP, but the peptide has been detected in the human fetal gonad.3 This is the first report of the presence of PTHrP in a hypercalcaemic ovarian carcinoma. While the pathophysiological role of PTHrP is yet to be elucidated, one possibility is that in addition to its inducing hypercalcemia it may stimulate the growth of tumour cells in an autocrine manner.4 It may also regulate the renal calcium balance.5

The widespread presence of PTHrP in lung, renal cell, and squamous cell carcinomas and its presence in small cell ovarian carcinoma, as reported here, suggests that PTHrP is a common manifestation of the transformed cell.

Prorenin in ovarian cyst fluid
Aspartic protease renin is secreted by the kidneys and, as the initial enzyme in the renin-angiotensin cascade, it is important in the regulation of blood pressure and fluid homeostasis. Recently, high concentrations of the zymogen prorenin have been found in female reproductive organs.6 The concentrations of prorenin in follicular fluid collected from women undergoing in vitro fertilisation are at least 10 times higher than those in plasma.7 Immunochemical staining has shown that the prorenin is present in the theca cells lining the follicles from where it is, presumably, secreted into the fluid.8 As only very low concentrations of active renin are found in the ovary, it has been postulated that ovarian prorenin may be biologically active without any necessity for prior removal of the propeptide sequence.9 The role of ovarian prorenin is still unclear but it probably operates through the formation of angiotensin II (AII). Studies with the AII antagonist, saralasin, have indicated a direct role for AII in ovulation,10 and, in addition to its effects on steroidogenesis, the vasconstrictor and angiogenic properties may be important for follicular growth.

Cysts are commonly derived from the ovarian follicles and frequently contain a large volume of liquid. It was thus considered of interest to determine whether this fluid might also contain a high concentration of prorenin. The fluid from one of the cysts removed at laparotomy was collected, stored at –20°C, and assayed for prorenin by the trypsin-activation method of McIntyre et al.11 Renin activity was estimated by measuring the rate of angiotensin I (A1) production from human angiotensinogen.

Prorenin was detected in the fluid from four of the cysts assayed—three of follicular origin and one from a mucinous cystadenoma. Two of the others being virtually negative (table). The concentration of active renin detected in all of the fluids was very low (less than 5% of total) and may have been due to partial activation of the prorenin during collection. This predominance of prorenin over renin is in keeping with previous results for normal ovarian follicular fluid.12

Concentrations of prorenin in ovarian cyst fluid

<table>
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<tr>
<th>Age</th>
<th>Diagnosis</th>
<th>Prorenin (ng A1/ml)</th>
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</thead>
<tbody>
<tr>
<td>18</td>
<td>Follicular cyst</td>
<td>41</td>
</tr>
<tr>
<td>20</td>
<td>Follicular cyst</td>
<td>41</td>
</tr>
<tr>
<td>42</td>
<td>Follicular cyst</td>
<td>24</td>
</tr>
<tr>
<td>44</td>
<td>Mucinous cystadenoma</td>
<td>15</td>
</tr>
<tr>
<td>52</td>
<td>Serous cystadenofibroma</td>
<td>1</td>
</tr>
<tr>
<td>83</td>
<td>Serous cystadenofibroma</td>
<td>0</td>
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References


Potential benefit of 1-alpha-cholecalciferol in hypomagnesaemia by cyclosporin.

C J Pearce and J M Davies

*J Clin Pathol* 1990 43: 783-784
doi: 10.1136/jcp.43.9.783-b

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