RATIONAL TESTING
Appropriate requesting of serum tumour markers

Eric S Kilpatrick, Michael J Lind

Tumour markers have a limited role, if any, in initial investigations, but they can be important in following up patients with known malignancy

The patient
A 54 year old woman presented to her general practitioner with swelling of her abdomen, general malaise, and weight loss of about 5 kg during the preceding three months. On examination, she had a slightly distended abdomen and evidence of ascites. No masses could be felt.

The general practitioner ordered routine biochemistry tests as well as requesting CA125, CEA (carcinoembryonic antigen), and CA19.9 tumour markers, as he believed these would help him judge the likelihood of ovarian, colonic, and pancreatic cancers. The results of these and routine biochemistry are shown in the table.

An urgent gynaecological oncology referral was arranged to exclude ovarian cancer. Both abdominal ultrasound and computerised tomography confirmed ascites, but showed no ovarian mass or intra-abdominal malignancy. However, the liver was atrophic and showed a diffuse surface irregularity. Subsequent testing found hepatitis C infection with hepatitis C virus RNA detectable in the serum, and a liver biopsy confirmed cirrhosis. The history included no obvious risk factors for the hepatitis C infection.

What should the next investigation have been?
This case highlights the limitations of using most serum tumour markers to help in the exclusion or diagnosis of malignancy. Ascites can be a feature of ovarian cancer, but CA125 measurement in its presence can be misleading, as any cause of serosal fluid can increase the marker’s serum concentration. Likewise, non-malignant liver disease can cause rises in both CEA and CA19.9. This patient was not as widely investigated as a previous case of raised CA125 presented in the BMJ, in which a further diagnostic laparoscopy, mammography, and oral gastroduodenoscopy was performed in a patient with ascites due to hypothyroidism.

Because of these and other limitations, none of the commonly requested tumour markers related to gastrointestinal and gynaecological disease (CEA, CA19.9, and CA125) is recommended for screening for cancer, and most expert groups also recommend against using them in the initial investigation of a patient who has symptoms. As a screening tool, the positive predictive value (PPV) of a raised CA125 concentration is estimated to be 2.3%, requiring 50 women to undergo laparoscopy or laparotomy for one ovarian cancer to be detected. CA125 was used as the initial screen in the UK Collaborative Trial of Ovarian Cancer Screening, which showed that repeated CA125 testing followed by transvaginal ultrasound may perform better, but such a strategy still required 4355 women to be recalled for further testing in order to diagnose 42 ovarian or tubal malignancies, and the effect of this detection on mortality remains unknown.

The use of these and other tumour markers as a panel of tests in patients with symptoms and undifferentiated clinical features who are suspected of having cancer (as was the case here) has not been as closely studied, presumably because of the variety of possible clinical presentations. However, retrospective audit evidence from our institution has confirmed that in patients suspected of having cancer normal results can be falsely reassuring for some patients (and may delay diagnosis), and raised values can be unduly alarming in others. Of further concern was the observation, in the same study, that a sixth of requests for CA125 and over a quarter of requests for CA15.3 (a marker of breast cancer) were not as widely investigated as a previous case of raised CA125 presented in the BMJ, in which a further diagnostic laparoscopy, mammography, and oral gastroduodenoscopy was performed in a patient with ascites due to hypothyroidism.

Results of routine biochemistry

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125</td>
<td>1450 kU/l</td>
<td>0-35 kU/l</td>
</tr>
<tr>
<td>CEA</td>
<td>9 µg/l</td>
<td>0-5 µg/l</td>
</tr>
<tr>
<td>CA19.9</td>
<td>69 kU/l</td>
<td>0-37 kU/l</td>
</tr>
<tr>
<td>Sodium</td>
<td>133 mmol/l</td>
<td>135-144 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6 mmol/l</td>
<td>3.5-5.3 mmol/l</td>
</tr>
<tr>
<td>Urea</td>
<td>2.0 mmol/l</td>
<td>2.1-7.6 mmol/l</td>
</tr>
<tr>
<td>Creatinine</td>
<td>93 µmol/l</td>
<td>51-167 µmol/l</td>
</tr>
<tr>
<td>Alkaline phosphate</td>
<td>138 µU/l</td>
<td>30-125 µU/l</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>27 µmol/l</td>
<td>7-23 µmol/l</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>61 µU/l</td>
<td>5-45 µU/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>32 g/l</td>
<td>36-48 g/l</td>
</tr>
</tbody>
</table>
Exacerbation of atopic eczema in children

Matthew Ridd, Sarah Purdy

A father attends with his 18 month old son Samuel because “his eczema is playing up”

What issues you should cover

Ask how long the patient has had eczema and what does his father already know about it? Ask what is meant by “playing up.” Specifically ask about itch and how the patient’s activities and sleep have been affected. Find out “playing up.” Specifically ask about itch and how the patient’s activities and sleep have been affected. Find out what you should do

Examine the patient to see how he is generally. See which areas of skin are affected. Look for dryness, redness, scratch marks, and infection. Confirm the diagnosis, remembering that the distribution differs between ages and ethnic groups. Distinguish site and severity from atopic eczema severity

Stepped approach for managing atopic eczema in children (adapted from the NICE guidelines)
the child for admission if you discover severe bacterial infection or eczema herpeticum.

Explain that atopic eczema is a common long term childhood condition that fluctuates in severity but often improves with age.

Advise on irritants to be avoided and that distraction or rubbing should be used in response to the patient's itching (to discourage the "itch-scratch" cycle). Say that the child's nails need to be kept short and that his bedroom should be kept cool. Advise that cotton bedding and specific clothing (such as pyjamas with mitts) might help.

Use a stepped approach to the use of emollients, topical steroids, and other treatments (see figure).

• Encourage regular emollient use, including in the bath. Encourage the parent to try different ones because "the correct emollient is the one that the child will use." Prescribe large quantities (250-500 g weekly) on repeat prescription—for use even when skin appears clear. Advise the parent to smooth on to skin in the direction of hair growth and not to rub it in.

• Prescribe topical steroids in ointment form for use once or twice daily. Advise the parent to leave a gap (up to 30 minutes) between applying emollient and topical corticosteroid. Say that they can expect improvements within 14 days.

• Advise that for flares on the face, genitals, or axillae, a strongly potent corticosteroid should not be used for more than five consecutive days.

• Prescribe short courses of moderate potency steroids rather than longer courses of low potency ones to minimise adverse effects. Most products come with an information leaflet describing the amount required in fingertip units. One fingertip unit, measured on an adult finger, treats an area equivalent to twice the size of an adult's hand with the fingers together.

• Advise that emollients and steroids should be used in the ratio 10:1.

• Consider prescribing chlorphenamine if the child's sleep is disturbed by severe itching or urticaria.

• Clinically infected eczema (pustules, weeping and crusting, or worsening eczema) benefits from treatment with antibiotics. Because of concerns about resistance, limit topical antibiotic combinations to short courses (typically one week). Prescribe oral antibiotics (flucloxacinllin or erythromycin if the patient is allergic to penicillin) for moderate to severe infections for seven days initially.

Encourage the parent to reduce house dust mites. Support verbal advice with written information, and arrange to see the child again.

Seek specialist advice when:

• You are uncertain of the diagnosis

• Serious psychosocial difficulties exist

• Control is poor—medicated dressings or bandages and topical calcineurin inhibitors may reduce topical steroid use

• You suspect food allergy—a recent Cochrane review concluded that an egg free diet in infants with egg allergy may be beneficial.

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“Pseudo-extubation”? 

Accidental extubation is a well recognised and potentially important complication during neonatal transport. With hindsight, the following incident—which occurred during transfer of an intubated term neonate for possible surgery—is amusing, but it does highlight the need for careful clinical assessment before reaching a definitive diagnosis.

While the transport incubator was being secured into the ambulance, muffled infant crying was heard coming from the incubator. Immediate review showed that the infant's heart rate and saturation were stable, but, given the pending transfer and ongoing sedation, the transport team began preparing for reintubation while reassessing the infant's condition. The infant remained stable, and the crying stopped at the same time as the ambulance technician stood up off the floor, having secured the transport incubator, and answered his mobile phone. On direct questioning, the ambulance technician confirmed that his mobile phone ring tone was a download of his new baby daughter crying. The baby being transferred did not require reintubation and was transferred safely.

We are now both very aware of external factors that might influence the apparent clinical condition of babies during transport.

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For clinicians


For patients

British Association of Dermatologists


For clinicians


For patients

British Association of Dermatologists


USEFUL REAdING
We report two cases of probable interaction between the commonly used anticonvulsant valproate and chitosan, a substance available worldwide to help weight loss.

A 35 year old woman with idiopathic generalised epilepsy, who had not had seizures for three years while taking valproate (500 mg twice/day; 52 μg/ml) and phenobarbital (75 mg/day), had the sudden reappearance of myoclonic jerks, absences, and a tonic-clonic seizure a few days after a dietary supplementation with chitosan (500 mg twice/day) for weight loss. She denied changing her diet and consuming other drugs or natural substances. Seizures remitted after chitosan was stopped. Three months later she restarted chitosan and within five days she had daily absences, myoclonus, and generalised abnormalities on electroencephalogram. Serum concentrations of valproate were undetectable despite regular intake of the drug, whereas phenobarbital remained at therapeutic concentration (20 μg/ml). Chitosan was discontinued. Seizures remitted and valproate concentration returned to baseline levels (50 μg/ml) within four days.

A 29 year old woman with idiopathic generalised epilepsy, who was treated with valproate (1250 mg/day; 65 μg/ml) and remained seizure free for two years, had two tonic-clonic seizures and daily absences after one week of chitosan supplementation (500 mg/day). No changes of the regular intake of antiepileptic treatment or consumption of any other drugs were reported. Valproate serum levels were undetectable and seizures promptly disappeared after chitosan was stopped.

The Naranjo probability scale confirms that chitosan treatment was the most likely cause of drastic lowering of valproate serum levels and the reappearance of seizures in these patients. In both women, the event remitted and valproate levels returned to the target range after chitosan was stopped.

Chitosan has been proposed as a safe and effective dietary supplement to aid weight loss by reducing the amount of absorbed dietary fat and thereby improving caloric balancing. Structurally, it is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acylated unit). The amino group has a pKa value of about 6.5 and chitosan acts as a positively charged polymer that binds to the negatively charged lipids in the gastrointestinal tract, preventing their absorption.

We think that the anionic carboxyl group of the lipophilic valproate may attach to the positive charged tertiary amino group of chitosan so that it is extracted by the suppressed enterohepatic recirculation of the drug because of the negative effect of chitosan on enteric bacteria.

This interaction has not been reported by the Italian Agency for Pharmaceuticals or by the manufacturers of chitosan. It is known, however, that chitosan can affect the absorption of fat soluble vitamins, and that the anti-coagulation effect of warfarin may be increased through the mechanism. As chitosan products are freely available, healthcare professionals should be aware of their potential interaction with all lipophilic substances.

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“What care I for a goose feather bed”

I worked for six months in 1958 as a house surgeon in obstetrics at Southampton General Hospital. The mothers from the Romany community in the nearby New Forest would have their babies delivered in the maternity unit, and then mother and baby would be transferred to the convalescent ward. This was a delightful sunny room with tall French windows opening on to a garden.

By the morning, the mother would have vanished, leaving the baby in the cot at the foot of the bed. The first time this happened I panicked, but the experienced ward sister told me not to worry. Sure enough, several nights later the baby quietly vanished back to the mother—to the fresh air of the forest.

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