Recurrent sulphaemoglobinaemia treated with neomycin

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In the first half of the twentieth century sulphaemoglobinaemia was associated mainly with use of aniline derivatives, sulphonamides and nitrates¹. Formed by the production of a ferrohaemoglobin-peroxide complex which is sulphated in the presence of hydrogen sulphide, sulphaemoglobin persists for the life of the red cell. The terms microbic cyanosis² and enterogenous cyanosis³ reflected the early belief that enteric organisms were involved in the pathogenesis.

CASE HISTORY

A woman aged 61 was investigated in 1985 for breathlessness and an iron deficiency anaemia. She had a history of farmer's lung. Upper gastrointestinal endoscopy showed oesophagitis; nothing abnormal was seen on colonoscopy. Breathlessness persisted despite correction of anaemia. In 1991, peripheral cyanosis was noted but was attributed to restrictive lung disease. In 1992 central cyanosis was seen; methaemoglobin was not detected and the combination of PO₂ 9.4 kPa with oxygen saturation 77% on room air suggested a reduced oxygen binding affinity of haemoglobin. By February 1994 the cyanosis had increased and sulphaemoglobin (SHb) was found by spectrophotometry to be 7.0% (normal 0–0.7%) of a total haemoglobin of 14.4 g/dL. The patient was taking regular paracetamol, dihydrocodeine, iron and omeprazole. Analysis of her drinking water showed no excess nitrate.

All drugs were stopped, but by May 1994 SHb had risen to 10.6%. From July 1994 she was treated with 2 g oral neomycin daily for six weeks, after we had found a case report of this treatment. By August SHb had fallen to 5.0%

and after a further four months it was 0.6% and symptoms had improved. In the subsequent year SHb fell to <0.1% without further treatment but by February 1997 it had risen again to 5.9%. After another six-week course of neomycin SHb was 1.4%. Over the next year SHb rose gradually to 3.9% and, despite eight weeks of neomycin, to 5.9%. After a further two months of treatment no SHb was detectable.

Stool samples were cultured on three occasions—April 1997, shortly after neomycin treatment, when SHb was near normal; in August 1998 with SHb 4.1% on neomycin; and in December 1998 off neomycin with no detectable SHb. Dilutions of faecal samples, down to 1 in 10⁻¹⁰, were cultured on selective and non-selective media, including anaerobic neomycin blood agar, for 48 hours. Isolates were identified to species level. The first specimen yielded an almost pure growth of antibiotic sensitive *Escherichia coli*. This organism did not have any unusual characteristics and did not produce hydrogen sulphide. The two later specimens contained mainly anaerobic faecal flora; no hydrogen-sulphide-producing organisms were found.

COMMENT

The use of neomycin in this case was prompted by the report of Rossi *et al.*⁴, on a patient with combined methaemoglobinaemia and sulphaemoglobinaemia treated on one occasion with neomycin⁴. There has since been a further report, of a patient from Denmark with combined methaemoglobinaemia responding to treatment with neomycin and bacitracin⁵. In our patient with recurrent sulphaemoglobinaemia the effect of the first two courses of neomycin seems clear; on the third occasion, delayed disappearance of SHb may have been attributable to normal clearance mechanisms. We wondered whether our patient's chronic use of paracetamol, with omeprazole acting as a sulphur donor, might have been the cause, but this explanation was ruled out by persistence of sulphaemoglobinaemia when the drugs were stopped. The patient differed from the two others reported, in not having a raised methaemoglobin. The response to poorly absorbed antibiotics suggests a bacterial mechanism in this type of cyanosis but we have been unable to identify the organism.

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Two patients with acute intermittent porphyria treated with nafarelin to prevent menstrual exacerbations

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Acute intermittent porphyria (AIP) often presents with recurrent attacks of abdominal pain and vomiting. Many stimuli can precipitate attacks, including menstruation.

CASE HISTORIES

Patient 1

The first patient, now aged 24, was originally diagnosed with AIP genetic trait at age 11, after family screening (Figure 1). Recurrent attacks of abdominal pains and vomiting (occasionally with headaches and leg pains) began at age 13.

Over the years, she had multiple acute attacks of abdominal pain, averaging 10–20 hospital admissions per year. There was well-documented evidence of raised porphyrin precursors during acute attacks and normal levels in between attacks (for example, during an attack urinary porphobilinogen [PBG] 310 $\mu\text{mol/L}$ [reference range 0–8.8] and aminolaevulinic acid [ALA] 275 $\mu\text{mol/L}$ [0.8–34.3]). As well as occasional unpredictable attacks, she would regularly experience an acute attack one week before menstruation. Typically this led to hospital admission for intravenous fluids, high carbohydrate intake and opioid analgesia; usually she stayed in hospital for 2 weeks per month. She required frequent pethidine or morphine, became depressed and required admission to the drug dependency unit for formal opioid withdrawal. She felt that her relationship with her 2-year-old son was seriously affected by the frequent hospital admissions.

In January 1996, after appropriate barrier contraceptive advice, she was started on nafarelin nasal spray 400 μg twice daily and referred for both dual emission X-ray absorption (DEXA) scan to measure baseline bone mineral density and

gynaecological follow-up of her endometrium. She became amenorrhoeic and the attacks of AIP resolved.

In the 3 years she has been receiving nafarelin she has been admitted 12 times with abdominal pain, at least 6 of the admissions being preceded by non-use of her nafarelin spray (usually because of nasal irritation); on two further occasions, attacks resumed within weeks of the introduction of oestrogen. Oestrogen was used in an attempt to confer bone protection without precipitating an AIP attack, but even when the transdermal route (Estraderm TTS patch 50 μg twice weekly) was used to avoid hepatic first-pass metabolism, acute AIP ensued. This left only 4 unaccounted attacks of AIP over the 3 years, compared with the 36 that would have been expected. She has been attack-free for eight months. She now awaits a repeat DEXA scan to assess any possible loss in bone mineral density.

Patient 2

The sister of patient 1, now aged 22, was originally diagnosed with AIP genetic trait at age 9. Attacks of abdominal pain began at age 11 years. These seemed less severe than her sister's and indeed she has only required hospital admission on 3 occasions. Again there was well-documented evidence of raised porphyrin precursors during the attacks with normal levels between attacks (for example, during an attack urinary PBG 497 $\mu\text{mol/L}$). She too experienced perimenstrual exacerbations, with severe abdominal pains for 3 days before menstruation and 2 days subsequently. After appropriate contraceptive advice she was started on nafarelin spray 400 μg twice daily and was referred for DEXA and gynaecological follow-up. She became amenorrhoeic and is currently attack-free at eight months.

COMMENT

The acute porphyrias are hereditary disorders of haem biosynthesis, with clinically overt disease in about 1–2 per 100 000 of the population of Europe¹. They lead to accumulations of the precursors of haem—ALA, PBG and porphyrinogens. Acute intermittent porphyria is an autosomal dominant inborn error of metabolism due to a defect in PBG deaminase. Most cases are silent and women are more likely to manifest acute attacks than men. 95% of cases are characterized by abdominal pain and vomiting, but psychiatric and neurological symptoms occur, with some attacks resulting in death. Alcohol, stress, starvation, infections, sex steroids (including the oral contraceptive pill) and many drugs that tend to increase ALA synthase activity can precipitate acute attacks.

Nafarelin, a decapeptide gonadotropin-releasing hormone (GnRH) agonist analogue, produces initial stimulation, and then with continued administration down-regulation of the pituitary gonadotropin-releasing hormone

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Figure 1 Family tree of patients 1 and 2

receptors, reducing the release of luteinizing hormone and follicular stimulating hormone and in turn androgen and oestrogen production. Indications for use of GnRH analogues include endometriosis, infertility, anaemia secondary to fibroids and cancer of the breast and prostate.

GnRH analogues have been used for prevention of cyclical attacks of AIP since 1984², but therapy has usually been short-term. Patient 1 has now been on treatment for thirty-six months and preservation of bone mass is increasingly an issue. GnRH analogues are currently recommended (UK licensing guidelines) for a maximum of six months' treatment because of detrimental effects on bone mineralization³, although there are data to suggest that further courses of treatment may have little further long-term detrimental effect on bone density⁴ and that concomitant administration of norethisterone may negate this effect⁵. Side-effects include menopause-like symptoms

such as flushing, vaginal dryness and reduction in breast size⁶.

Both our patients were greatly relieved by treatment with nafarelin, and each withdrawal of the treatment led almost immediately to an attack of AIP (with hospital admission in patient 1). Both are keen to continue treatment. The potential drawback of this highly effective treatment is osteoporosis secondary to oestrogen deficiency. Low-dose oestrogen replacement therapy, by either the oral or the transdermal route, precipitated AIP attacks in patient 1 but other bone-conserving therapies such as bone-specific oestrogens or bisphosphonates remain an option.

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Pancreatic tumour with jaundice: good prognosis

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Papillary cystic epithelial neoplasms of the pancreas (PCENP) are rare tumours that appear in women in the

second or third decade of life. They are easily mistaken for more sinister neoplasms.

CASE HISTORY

A high-school girl, aged 15, was admitted for evaluation of a cholestatic syndrome (direct bilirubin 128 μ mol/L, alkaline phosphatase 640 U/L, alanine aminotransferase 60 U/L). Nothing abnormal was found on abdominal examination but a computed tomographic (CT) scan revealed a well circumscribed mass, 5 cm in longest diameter, in the head of the pancreas, partly cystic and partly solid (Figure 1).

At laparotomy the tumour was found to have a capsule and to be displacing rather than infiltrating the adjacent tissues. The common bile duct (CBD) was distended. The tumour was mobilized from the adjacent duodenum and inferior vena cava and enucleated without difficulty from

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Figure 1 Preoperative contrast enhanced computed tomographic scan

Figure 2 Resection specimen. Haematoxylin and eosin stain, × 230

the head of the pancreas. Because of the deep jaundice and the chronic external pressure on the intrapancreatic portion of the CBD the operation was completed with a choledochoduodenostomy. On histological examination the pancreatic lesion proved to be a papillary cystic tumour which was completely non-infiltrative (Figure 2). The resection margins were tumour-free. 5 years postoperatively the patient remains in excellent health, without

clinical or radiological evidence of local recurrence or distant metastasis.

COMMENT

Only 157 cases of PCENP have been reported since the first description by Frantz in 1959¹. Before then, and perhaps also since, these tumours may sometimes have been mistaken for adenocarcinoma of the pancreas²—hence the long survivals in occasional patients with supposed adenocarcinoma. The mean age of appearance is 21.8 years and half the patients are under 19³. Only 8 male patients have ever been reported⁴.

With most PCENP, the characteristics are those of a benign or low-grade-malignant tumour. In 21 of the 157 cases the behaviour was more aggressive, with infiltration of surrounding tissues or metastases⁵. The predominance of young women points to a hormonal influence; the histogenesis is unknown, but a neuroendocrine derivation is possible since neuron-specific-enolase-positive granules have been identified.

The possibility of PCENP should always be considered when a cystic pancreatic mass is discovered in a young woman. Complete surgical cure of this neoplasm is feasible by resection with disease-free margins.

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Pancreaticoduodenectomy after downstaging of pancreatic carcinoma by chemotherapy

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Surgery, the sole curative intervention in pancreatic carcinoma, is suitable in only 5–25% of patients and gives a 5-year survival of <15%¹. The Gastrointestinal Tumor Study Group has shown better median and 5-year survival in patients treated with postoperative chemoradiation than in those treated by surgery alone². Current efforts are focused on neoadjuvant chemoradiation³.

CASE HISTORY

A previously fit woman of 49 was referred with upper abdominal pain and obstructive jaundice. Ultrasound scanning showed an enlarged liver, dilated common bile duct and pancreatic duct, and cholelithiasis. At endoscopic cholangiopancreatography a friable and irregular mass was seen protruding through the ampulla, and a biopsy specimen was reported as villous adenoma with moderate dysplasia. A stent was placed in the common bile duct. The tumour marker CA 19-9 proved to be raised, at 650 U/mL (normal <34). A computed tomography (CT) scan showed enlargement of the pancreatic head, and selective angiography excluded arterial and portal vein involvement. A laparotomy was performed with a view to pancreaticoduodenectomy. At operation, the pancreatic head was mobile but there were several enlarged peripancreatic lymph nodes. Frozen section showed adenocarcinoma in one of these; therefore, palliative triple bypass was performed. Postoperatively the patient received six cycles of epirubicin, cisplatin and 5-fluorouracil (ECF), and the CA 19-9 fell to 215 U/mL. The CT scan was unchanged.

In view of the fall in CA 19-9, and after multidisciplinary discussion, a further laparotomy was undertaken for possible pancreaticoduodenectomy. The enlarged lymph nodes seen at the previous laparotomy were not evident and there was no sign of metastatic disease; the procedure was therefore performed. The operative specimen showed a 2 cm solid ill-defined grey lesion clear of the resection margins, reported as an infiltrating moderately differentiated adenocarcinoma; eight identified lymph nodes were clear of metastasis. The patient remains well 33 months postoperatively, with a CA 19-9 of 83 U/mL.

COMMENT

Pancreaticoduodenectomy carries a mortality rate of 2–3% and a complication rate of 25–35%. Since no survival benefit has been shown for patients with margin-positive resection specimens³ accurate preoperative assessment is therefore important. Furthermore, palliative pancreaticoduodenectomy for patients with advanced local disease is not proven superior to endoscopic stenting⁴. Exploratory laparotomy is now indicated only in patients with potentially resectable disease. The M D Anderson Cancer Center criteria for resectability⁵, which our patient misleadingly met, have a predictive value of 88%.

After the bypass operation, chemotherapy was offered with palliative intent. We know of only one study, involving 35 patients, of ECF therapy in pancreatic carcinoma. Median survival was increased by a quarter in patients whose unresectable tumour remained either static (62%) or regressed (17%)⁶. In our patient, a positive response was reflected in the fall in tumour marker. Since the ultimate result was downstaging of disease to node-negative status, the regimen can be regarded in retrospect as neoadjuvant.

Synchronous radiotherapy was not used in this patient, but neoadjuvant chemoradiation does seem to have advantages. The M D Anderson Cancer Center⁴ has shown that preoperative synchronous 5-fluorouracil and external beam radiotherapy is tolerable and about 56% of patients with potentially resectable lesions undergo pancreaticoduodenectomy with clear margins. The results also indicate an increase in median survival, to 19 months, though 4-year survival is only 19%.

The Fox Chase Cancer Center¹ has been using 5-fluorouracil and mitomycin C preoperatively (20–30% of patients experience side-effects that necessitate treatment breaks). Coia *et al.* conclude that there is downstaging of positive margins and of nodal metastasis and an increase in resectability rates. Survival at 1 and 3 years rose from 36% and 19% to 60% and 43%. Clearly, the value of neoadjuvant treatment deserves further exploration in

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potentially resectable pancreatic carcinoma. Randomized controlled trials are the best way to obtain the answers.

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