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Short communication

Fanconi syndrome after ifosfamide

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Summary. A 2-year-old boy developed the Fanconi syndrome 1 year after being treated successfully for a neuroblastoma. This is probably an unusual complication of ifosfamide.

Introduction

Ifosfamide is a cytotoxic drug widely used in the treatment of solid tumours in adults and children [1]. Initially the dose was limited because of the occurrence of haemorrhagic cystitis due to the local action of ifosfamide on the urinary tract epithelium. However, this can be prevented by the concurrent administration of mesna [1] and large doses can now be given safely. We report the case of a child treated with ifosfamide, who developed renal damage despite the concurrent administration of mesna.

Material and methods

A boy presented on his first birthday with a mass in the left side of his abdomen that had been enlarging for the preceding 2.5 months. The mass extended from the ribs to the umbilicus, from the flank to the midline. His blood pressure was elevated at 150/90 mm Hg, but the liver was not enlarged. Ultrasound examination showed a renal mass suggestive of a Wilm's tumour, and i.v. pyelography was thought to confirm this. His chest radiograph was normal.

At laparotomy a large intra-hilar tumour, invading posteriorly and crossing the midline, was found and removed. Multiple nodes were involved but the other kidney and liver were normal. At macroscopic examination the tumour appeared to be situated in the renal hilum, and microscopic examination showed that it was a poorly differentiated neuroblastoma. The adrenal gland was normal, and tumour was present in the lymph nodes but not the large hilar vessels. The kidney contained numerous foci of tumour, but the renal substance was normal.

As a bone scan and bone marrow examinations were normal, the tumour was classified as stage III and chemotherapy began, consisting of two courses of ifosfamide and mesna and six of OPEC.

Ifosfamide (3 g/m^2) was infused over 1 h together with 1.2 g/m^2 mesna before and 2.4 g/m^2 over the ensuing 24 h. This was repeated the next day, and 2 weeks later two further treatments were given. The patient received a total of 12 g/m^2 ifosfamide and the same amount of mesna. Hydration was maintained with 3 l/m^2 dextrose saline every 24 h. OEPC consists of i.v. 600 mg/m^2 cyclophosphamide and 1.5 mg/m^2 vincristine on day 1, on day 2 60 mg/m^2 cisplatin and 150 mg/m^2 teniposide on day 4. For the first 2 days, 3 l/m^2 dextrose saline is given daily.

^{51}Cr-EDTA clearance, serum electrolytes, calcium and magnesium levels and full blood count were normal before each course of treatment. On two occasions after chemotherapy the patient became febrile while neutropenic, and after specimens had been taken for culture he was treated with 2 mg/kg gentamicin and 65 mg/kg piperacillin three times a day. The gentamicin peak was 7.2 mg/l and the trough was 1.1 mg/l and 0.8 mg/l on each occasion, treatment being stopped after 7 and 2 days, respectively, as cultures were sterile and the neutropenia was resolved. A second-look laparotomy 6 months after presentation showed no local recurrence and there was no evidence of metastases.

The patient remained well, with normal chest radiographs and abdominal ultrasound examinations until 14 months after diagnosis, when he complained of pain in his legs. A bone scan showed no metastases, but careful review of a chest radiograph showed slight changes of rickets at the end of the humerus, confirmed by finding florid rickets at the wrist. His alkaline phosphatase was 1471 IU/l, serum phosphate 0.86 mmol/l, calcium 2.3 mmol/l, bicarbonate 19 mmol/l, magnesium 0.19 mmol/l, and creatinine 141 mmol/l. The patient had generalised aminoaciduria, proteinuria and glycosuria, and phosphate reabsorption was only 76% (normal, >85%). His ^{51}Cr-EDTA clearance was 48.6 ml/min per 1.73 m^2 and serum 25 hydroxycholecalciferol was 6.7 ng/ml (normal, 3–30 ng/ml). These results showed that he had developed the Fanconi syndrome, and he was treated with oral phosphate and 1 α-hydroxycholecalciferol. The rickets has healed but still requires treatment and urinary abnormalities persist 18 months later.

Discussion

This child developed the Fanconi syndrome, manifest by proteinuria, glycosuria and aminoaciduria, together with impaired phosphate reabsorption and low serum bicarbonate. He has rickets that still require treatment, and the urinary abnormalities persist.

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The aetiology of the Fanconi syndrome is uncertain. Tumour rickets is very unlikely, as hyperphosphaturia resolves when the tumour is removed [4]; thus it is probably drug-induced. Of the nephrotoxic drugs used, cisplatin causes a fall in glomerular filtration [6] and gentamicin causes a reversible decline in glomerular filtration as well as occasionally acute tubular necrosis [3], but neither is known to cause the Fanconi syndrome. Ifosfamide has been reported to cause transient proximal renal tubular failure [2], and there has been one case of prolonged renal tubular insufficiency [5]; it therefore seems probable that in our case the Fanconi syndrome was due to ifosfamide. The patient had a relatively small dose, matched by mesna, and it is likely that this was an idiosyncratic reaction rather than a dose-related side effect.

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