IFOSFAMIDE INDUCED RICKETS WHICH IS REVERSIBLE FOLLOWING TREATMENT:

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ABSTRACT

Ifosfamide is a derivative of cyclophosphamide used in the treatment of malignant tumors both in child and adult. One of its side effect is nephrotoxicity. A 5 years old child who received ifosfamide for treatment of retroperitoneal rhabdomyosarcoma subsequently developed hypophosphatemic rickets which improved with phosphate supplement is described.

Key Words: Ifosfamide, Fanconi's syndrome, Rickets.

INTRODUCTION

Ifosfamide is an oxazophosphorine derivative of cyclophosphamide and is currently used in the treatment of childhood rhabdomyosarcoma and other malignancies. It is widely used because of its low bone marrow toxicity and its treatment of cyclophosphamide resistant tumor.

Adverse effects of ifosfamide include nausea, vomiting, alopecia, myelosuppression, central nervous system toxicity, haemorrhagic cystitis and nephrotoxicity (1). Hypophosphatemic rickets has been recognized as an additional complication of ifosfamide treatment (1,2,3,5). We report a child with reversible hypophosphatemic rickets but an irreversible Fanconi's syndrome following treatment with ifosfamide.

CASE REPORT

A 5 years old Indian boy with retroperitoneal rhabdomyosarcoma stage IV and renal failure secondary to compression of ureters by tumor bilaterally, received post operative chemotherapy for almost 12 months. The chemotherapy consisted of vincristine, adriamycin and ifosfamide in combination with other chemotherapeutic drugs. He responded well to the treatment. Seven months after completion of chemotherapy his mother noticed that his eyes were puffy in the evening. Radiographs of chest showed cupping of the anterior end of the ribs which is characteristic of rickety rosary. (Fig. 1a) The wrist changes were also typical of rickets with widened growth plate, fraying, splaying and cupping of the metaphysis to surround the uncalcified growth plate. (Fig. 1b) Laboratory investigations revealed an elevated alkaline phosphatase and lower end normal limits of calcium and phosphate. Serum creatinine and urea were elevated. The parathyroid hormone level was within the normal range. (See table 1)

Urine analysis showed aminoaciduria (mainly cysteine), mild proteinuria, glycosuria, calciuria and phosphaturia. (See table 2) Following treatment with oral phosphate supplement the serum concentration rose back to normal. Follow up radiographs also showed healing of rickets. (Fig. 2a&b).Urine examination showed a persisting disturbance of urine excretion which is suggestive of proximal tubular dysfunction.

DISCUSSION

The patient described, had rachitic changes thought to be caused by nephrotoxicity of ifosfamide.

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The specific features include abnormal urinary excretion of amino acids, phosphate, bicarbonate, glucose and small protein otherwise known as Fanconi's syndrome. The renal toxicity is predominantly tubular, although glomerular abnormalities may occur (1). Renal damage is usually irreversible (3) although reversible renal tubular dysfunction has been described (7).

There have been several recent report of development of Fanconi's syndrome with or without associated rickets (1,3,5). It has been shown that the total dose of ifosfamide received correlated with the severity of nephrotoxicity. It has also been suggested that the younger age may be a risk factor (8). Although it is thought that the toxic effect of ifosfamide is cumulative, Fanconi's syndrome may occur after a single dose of ifosfamide (9).

Rickets in Fanconi's syndrome is related to phosphate deficiency and in some cases to impaired conversion of 25-OH vitamin D3 to 1.25-OH vitamin D3. This in turn will cause a decrease in gastrointestinal tract absorption of calcium. A decrease in serum calcium will cause secondary hyperparathyroidism. In contrast, ifosfamide causes renal phosphate wasting with no effect on serum calcium level. An interesting observation made in this boy was the rachitic changes were reversible following treatment with oral phosphate supplement.

Therefore early detection of impaired renal function by close monitoring of serum and urine during and after ifosfamide therapy will allow earlier detection of Fanconi's syndrome and development of bone disease. The radiologist should also be attuned to the possibility of rickets when examining radiographs obtained for tumor surveillance.

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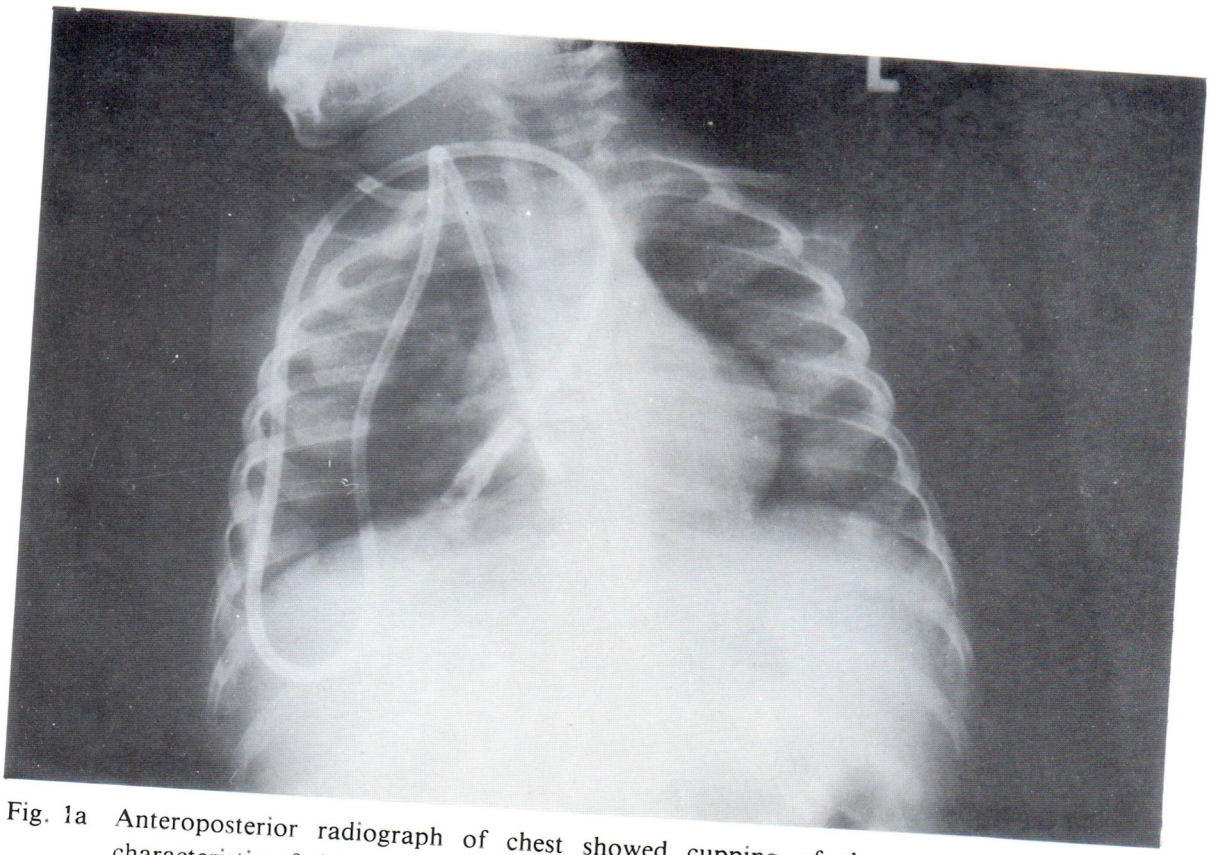

Fig. 1a Anteroposterior radiograph of chest showed cupping of the anterior end of ribs characteristic of rickety rosary.

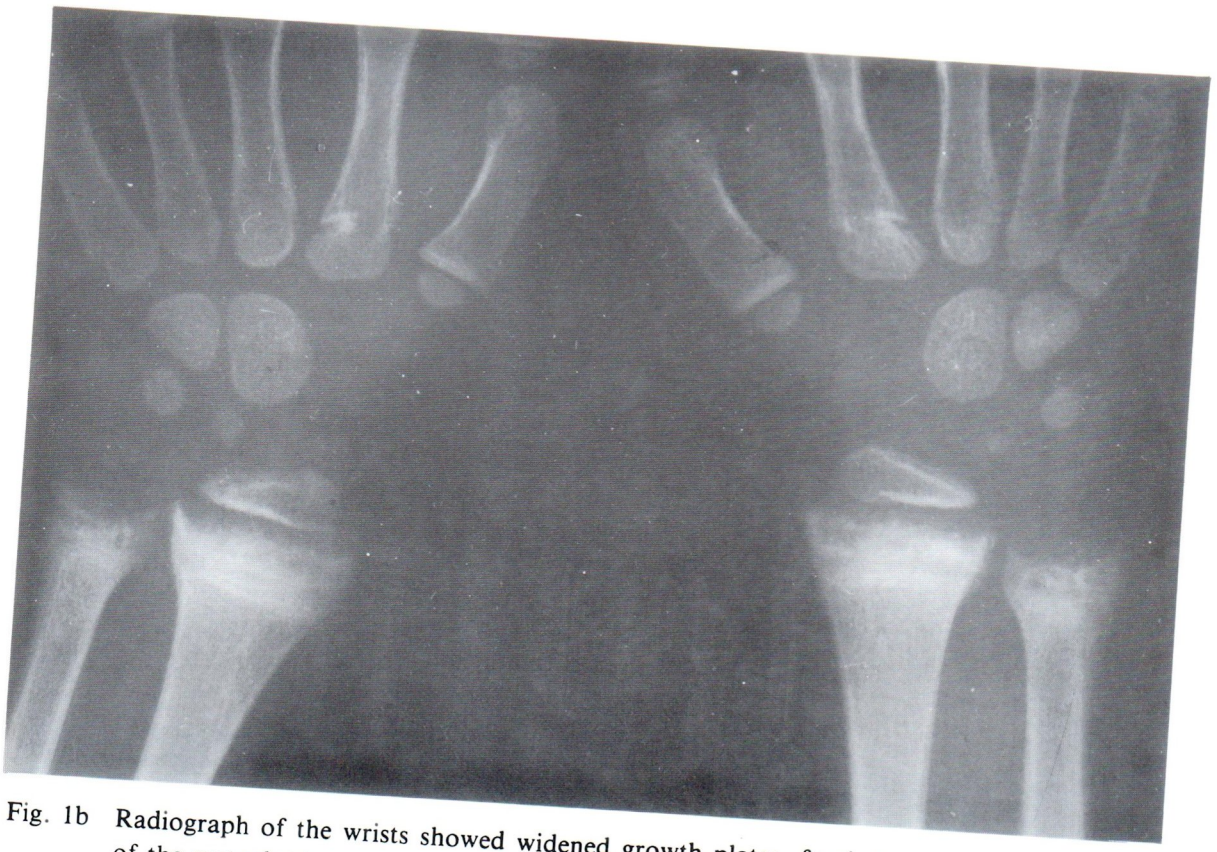

Fig. 1b Radiograph of the wrists showed widened growth plates, fraying, splaying and cupping of the metaphysis to surround the uncalcified growth plates.

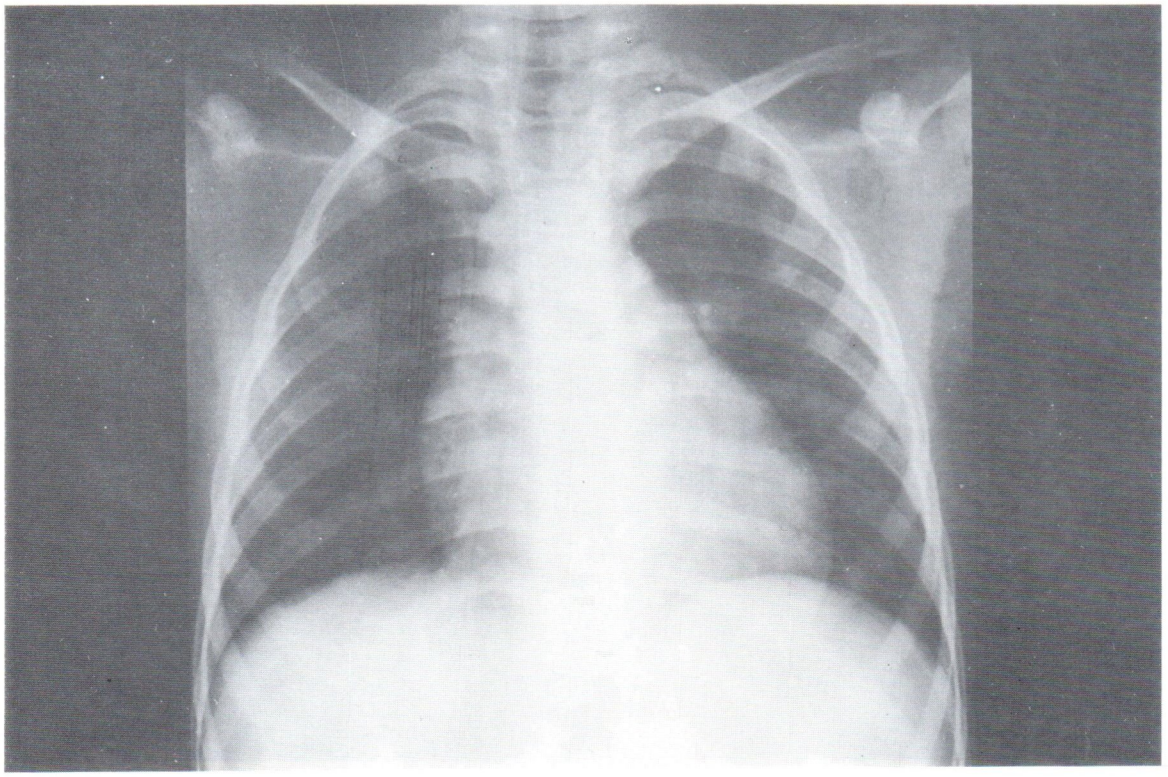

Fig. 2a Post treatment with oral phosphate radiograph of the chest, reveal healing of the rickets.

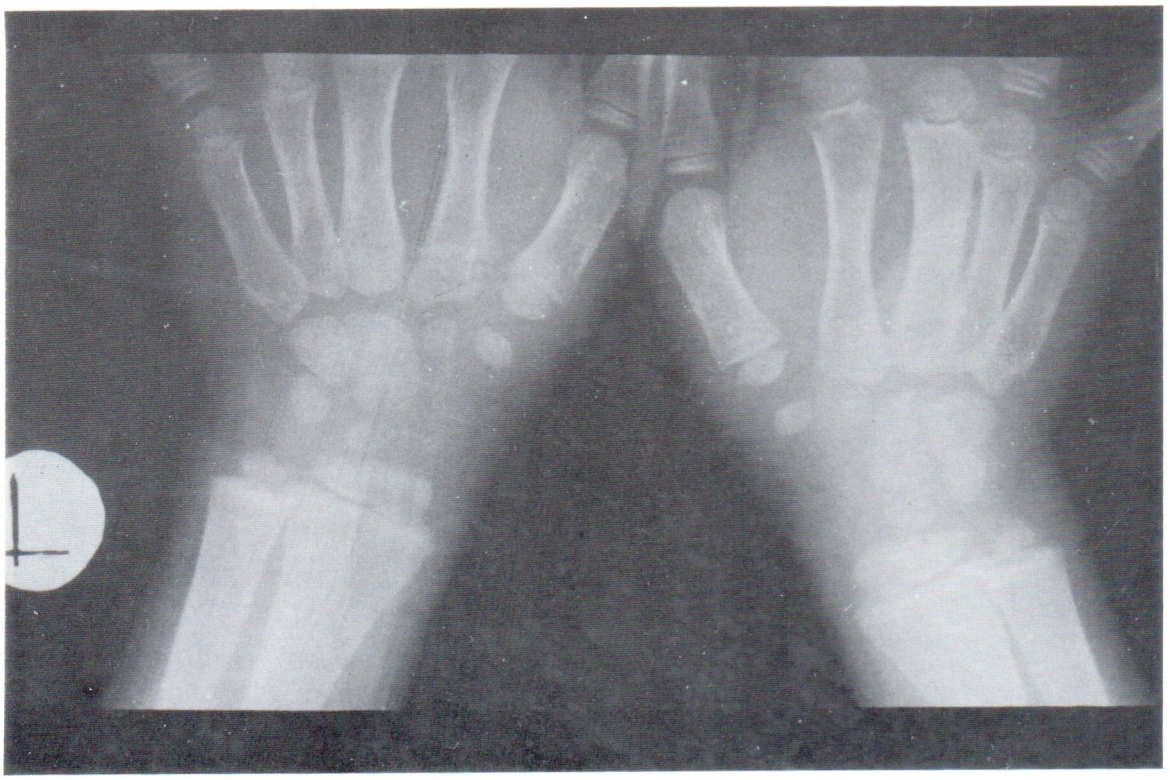

Fig. 2b Radiograph of the wrists reveal resolution of rickets after oral phosphate therapy.

Table-1 Evaluation of serum studies indicating renal tubular dysfunction in a 5 year old child.

SERUM	April 1993	August 1995	Normal range
Alkaline phosphatase	677 iu/L	371 mmol/L	0
Caicium	2.3 mmol/L	2.5 mmol/L	2.1-2.5 mmol/L
Phosphate	0.7 mmol/L	1.7 mmol/L	0.6-1.4 mmol/L
Creatinine	112 mmol/L	89 mmol/L	80-133 mmol/L
Urea	7.2 mmol/L	8.3 mmol/L	3.2-6.8 mmol/L
Potassium	2.3 mmol/L	3.2 mmol/L	3.5-5.3 mmol/L
Chioride	104 mmol/L	109 mmol/L	93-108 mmol/L
Bicarbonate	14 mmol/L	20.8 mmol/L	24-323 mmol/L
Base excess	-10	-4.1	-2- +2
Parathyroid hormone	4.9 pmol/l		1.1-6.5 pmol/L
Glomerular filtration rate	51 ml/min/1.73 metre squared		124ml/min/1.73 metre squared

Table-2 Urine analysis of a child with Fanconi's syndrome

24 Hours urine collection		Normal
Protein	0.52 gm/24 hrs	0-0.1 gm/24 hrs
Calcium	0.4 mmol/24 hrs	2.5-7.5 mmol/24 hrs
Phosphate	8.3 mmol/24 hrs	15-50 mmol/24 hrs
Creatinine	1.4 mmol/24 hrs	1.4 mmol/24 hrs

Urine analysis	1993	1995
Protein	+	Trace
Glucose	4+	2+
PH	6	9