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SHORT COMMUNICATION

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Nephrolithiasis in a worker with cadmium exposure in the past

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Abstract *Objectives*: A clinical case regarding a cadmium-exposed worker is described. *Clinical case*: The subject during the work as welder (male, 42-years-old at the time of the first investigation) developed a Fanconi-like syndrome due to high exposure to cadmium fumes. Ten years after exposure removal, the subject showed clinical and laboratory evidence of nephrolithiasis (calcium phosphate stones). *Conclusions*: The clinical case confirms the possibility of nephrolithiasis in cadmium-exposed workers and suggests that susceptible subjects may develop kidney stones after lesion of the tubular cells.

Keywords Cadmium · Welder · Nephrolithiasis

Introduction

Nephrolithiasis is a common disease, typically occurring between 30 years and 60 years of age (Preminger 1992). The formation of a clinically significant kidney stone requires a number of predisposing events, including urine supersaturation, microcrystal formation, further crystal growth, and maturation of the kidney stone. It has been shown on kidney epithelial cells in culture that the binding of crystals onto them is enhanced by prior cell injury (Lieske and Toback 1996). A direct relationship between apoptosis and crystal attachment has not been examined, but some correlative evidence has been reported suggesting that the two phenomena could be related in renal epithelial cells exposed to high oxalate levels (Khan et al. 1999).

Rarely the role of environmental and industrial pollutants has been considered, but an epidemiological study (Nuyts et al. 1995) supports their involvement in kidney stone formation. Among pollutants, it was suggested (Ishido et al. 1998) that cadmium produces biochemical and morphological alterations in kidney, which are characteristic features seen in apoptosis. Experimental studies (Fahin and Khare 1980) showed that injection of cadmium caused an increase in incidence of stone formation in the kidney and urinary bladder of male rats. Epidemiological studies in workers exposed to cadmium (Elinder et al. 1985; Jarup et al. 1997) showed that a history of renal stones was significantly more common in workers with high cadmium level. In addition, a dose–response relationship was found between cumulative exposure to cadmium and kidney stones (Jarup and Elinder 1993) and 40% stone prevalence in a cadmium-exposed group as compared with 3.5% in general population (Scott et al. 1982).

The aim of the present research is to describe and discuss the clinical and laboratory evidence of kidney stone in a worker with a history of cadmium exposure in the past.

Case report

Some years ago we published a clinical case on a welder, exposed to high cadmium concentrations at work (Trevisan and Bonadonna 1984). The welder developed a typical acquired Fanconi-like syndrome with aminoaciduria, enzymuria and low molecular weight proteinuria. Table 1 summarizes some data from the previous report. Histological findings (Trevisan and Bonadonna 1984) showed (light microscopy) a slight mesangial hyperplasia and (electron microscopy) proximal tubule cell brush border particularly rich in microvilli, with a great number of cytoplasmtic lysosomes. No other cadmium-

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Table 1 Indices of dose and renal function at the time of disease discovery

Index	Unit	Reference values	Values
CdB	μg/dl	< 0.1	4.14
CdU	μg/g creat.	< 1.0	90.8
TUP	mg/g creat.	< 200	967
Urinary albumin	mg/g creat.		154.7
Urinary ß$_2$MG	mg/g creat.	< 0.2	58.879
Aminoaciduria	mg/24 h	227.7–1363.5	2104.2
Urinary GGT	U/g creat.	< 30.0	55.0
Urinary ACE	U/g creat.	< 50.0	141.3

ß$_2$*MG* ß$_2$-microglobulin, *ACE* angiotensin converting enzyme

associated pathology was observed, in particular no glomerular, bone, lung or prostate alteration. At the time of investigation (1982), the subject (male) was 42-years-old with an exposure history of 20 years as welder. During the work, the values of cadmium concentration in air (personal sampling) were 1.16 mg/m^3 without and 0.22 mg/m^3 with aspiration devices. The historical A.C.G.I.H. TLV for cadmium was 0.05 mg/m^3 (now, 2004 TLVs, 0.01 mg/m^3). Table 2 reports data on biological indices of dose [cadmium in blood (CdB) and cadmium in urine (CdU)] and effect [total urinary proteins (TUP)] reckoning from the first discovery of cadmium disease. Metal in blood and urine was determined by means of atomic absorption spectrophotometry (Ross and Gonzales 1974), whereas TUP were determined according to Pesce and Strande (1973). Since 1982, the subject was removed from exposure. Interesting to note that after 20 years, the exposure indices lasted higher than reference values, in particular CdU. Accordingly, a mild proteinuria is persistent and since 1994 it is possible to observe a tendency to increase. In addition, calciuria (480 mg/24 h) and phosphaturia (1,200 mg/24 h) were observed, despite a normal intake of proteins (about 1 g/kg/day). Glomerular filtration rate appeared in the normal range (1982 and 1996), even if near to lower limit.

In 1992 (10 years after exposure removal), the subject observed the sudden onset of renal fret. Renal echography showed three stones (two at upper and one at lower pole of the kidney, diameter 0.5 cm approx.). In 1996, he was submitted to extracorporeal shock wave lithotripsy with neutron bombardment. Notwithstanding this, subject followed to have repeated (3–4 incident per year) renal fret and the last renal echography (2003) showed stone images in the upper and lower left kidney and in the middle right kidney calyx. The calculi were composed by calcium phosphate, and showed a crumbly consistence, a white-greyish colour, with the tendency to assume the form of a stamp. The patient denied familiarity for kidney stones.

Table 2 Indices of dose and renal function from 1982 (time of disease discovery) to 2003

Index	Unit	Reference values	1982	1988	1993	1996	2003
CdB	μg/dl	< 0.1	4.14	2.40	1.00	0.60	0.70
CdU	μg/g creat.	< 1.0	90.8	48.1	27.2	16.5	12.00
TUP	mg/g creat.	< 200	967	860	666	1,078	1,920
Urinary ACE	U/g creat.	< 50.0	141.3	84.0	ND	ND	ND
GFR	ml/min	70–140	100	ND	ND	76	ND

ACE angiotensin converting enzyme, *GFR* glomerular filtration rate, *ND* not determined

Discussion

The evidence of renal stones in a worker with cadmium exposure in the past confirms the possibility that cadmium is a causal factor in the development of nephrolithiasis (Elinder et al. 1985; Jarup et al. 1997). The subject presented high CdB and CdU levels, tubular damage (aminoaciduria, enzymuria, and low molecular weight proteinuria) onset approximately 20 years after the beginning of the exposure to cadmium. Histologically, the tubular damage appeared mild, even if the increase in enzyme, proteins and amino acids excretion supported the clinical diagnosis of acquired Fanconi-like syndrome. Surprisingly, a history of kidney stone was clinically evident 10 years after exposure cessation and 30 years after the exposure start. In addition, calciuria and phosphaturia are typical expression of kidney involvement by cadmium and a cause of the bone metabolism disturbance (Kazantzis 2004). Lacking a history of nephrolithiasis in patient's family, without cadmium exposure the subjects should have the same risk of kidney stones of the general population, where the frequency is about 17/1,000 inhabitants (Amato et al. 2004), fourfold more frequently in males, matched for age, gender, and environmental conditions.

In conclusion, the long and high cadmium exposure is most likely the cause of nephrolithiasis. We have the opinion (Gambaro et al. 2003) that subjects with congenital or acquired susceptibility may develop clinically evident kidney stones, if minimal lesions of tubular cells are induced by toxic (environmental and/or industrial) hit.

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