ADRENAL GLANDS MORPHO-FUNCTIONAL DAMAGES AT WISTAR RATS AFTER CHEMOTHERAPY ADMINISTRATION

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ABSTRACT. Most of cancer drugs used in chemotherapy induce most of the time strong immunosuppresive states and lymphotoxic effects, characterized especially by the alteration of lymphoid tissues. The aim of this study is to reveal stress conditions adrenals response after given chemotherapy as the connections between immune and endocrine system are well known. Giving 40 mg/kg body/day cyclophosphamide (CFA) therapy to rats by 3 days consecutively i.p. injections, can determine morphological and structural damages of the studied organs. The 24 hours adrenals histopathological and electron microscopy examination after CFA last dose administration proved the installations of some structural changes especially in the glomerulosa and fasciculata zone of adrenal cortex.

Keywords: cyclophosphamide, adrenal glands morpho-functional damages

INTRODUCTION

For cancer chemotherapy, the use of cancer drugs induces most of the times unwanted side effects, altering the metabolic functionality of some healthy tissues and organs (immunotoxicity, neurotoxicity, immunosuppression). The administration of some cytostatics with immunosuppressive and strong lymphotoxic effects, like cyclophosphamide or cisplatin, can induce several side effects on the immune system (Blank et al, 1991; Luster et al, 1993; Pasca et al,2000).

MATERIAL AND METHODS

Antitumoral drug

Jenapharm, Ankerwerk-Germany Ciclofophosphamide (CFA), was before deluted in a 0,9% sterile physiologic Na Cl solution and intraperitoneal animals injected for 3 days.

Animals

The experiments were made on white male Wistar rats, weighting 170-180 g, kept under standard diet and conditions.

The following animal groups were used: control group (M); group treated with Cyclophosphamide (40 mg/kg body/day) administrated by intraperitoneal injections for 3 days;

The animals were sacrificed after finishing the treatment at 24 hours , respectively at 14 days Cyclophosphamide first dose given.

Histopathological analysis

Adrenal samples were collected into PBS and fixed overnight in 40 g/L paraformaldehyde in PBS at 4 °C. Serial 5-µm sections of the organs were stained with hematoxylin and eosin (HE), and were examined histopathologically.

Biochemical investigation

Cholesterol was achieved (Kovacs, 1956) and C Vitamin from adrenal glands (Klimov & Asatiani method, 1957) from adrenal tissue homogenate in 0,32 M sucrose.

RESULTS

Organ weights

After CFA administration absolute and relative weight of adrenals obviously increases as we can notice in table 1.

Table 1

DEVELOPMENT OF SOME ADRENALS ABSOLUTE AND RELATIVE WEIGHTS OF RATS TREATED WITH CYCLOPHOSPHAMIDE (CFA)

ADRENAL GLANDS WEIGHT	CONTROL	CFA
Absolute weight	**43,08±0,99**	**45,35±0,99**
	(6)	**(7)**
	-	**+5,26**
	-	**p>0,25**
Relative weight	**22,21±2,32**	**23,78±0,57**
	(7)	**(7)**
	-	**+7,06**
	-	**p>0,25**

Histopathological results

Discrete morphological changes can be seen after 24 hours since the last CFA administration and they are translated as as cytoplasmic vacuolization which can be noticed among a part of cells belonging to adrenal cortex and medulla, but their number is not high. Most affected seem to be cells from gromerulosa zone from adrenal cortex (fig.1). However, this zone is a bit thinner in comparison with the control (fig.2).

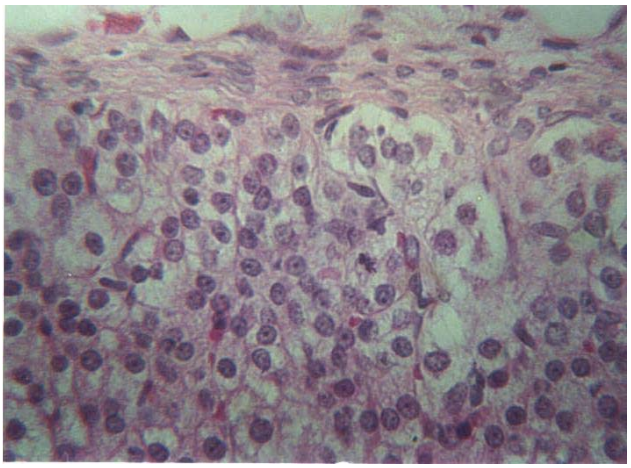

Fig. 1 Cytoplasmic vacuolization of glomerulosa adrenal cortex zone after CFA therapy, col.H.E. (x40)

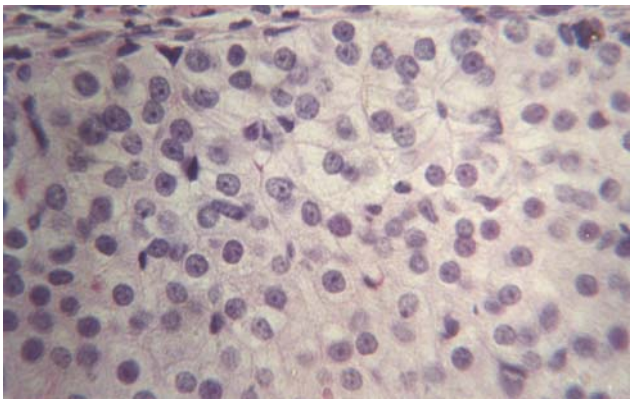

Fig. 2 The aspect of glomerulosa zone at control group, col. H.E. (x40)

There are no ultrastructural semnificative changes in comparison with the control, neither on the adrenal electron microscope micrographs of CFA treated rats.

But, some aspects are recorded at the level of fasciculata zone which may show some ultrastructural damages.

The steroid hormone structure make some different changes and this represents decreasing of hormone synthesis activities. There are zones with hormone granules which are intracellulary stocked and accumulated (fig.3).

The fasciculata zones cellular nuclei appear with a stressed irregular outline (fig 3).

Most of mitochondria are normal, small, with lamellar or tubular cristae (fig.4).

Biochemical results

We can take notice that at CFA treated rats both suprarenal cholesterol and C vitamin amount are a bit raised in comparison with the control (table 2).

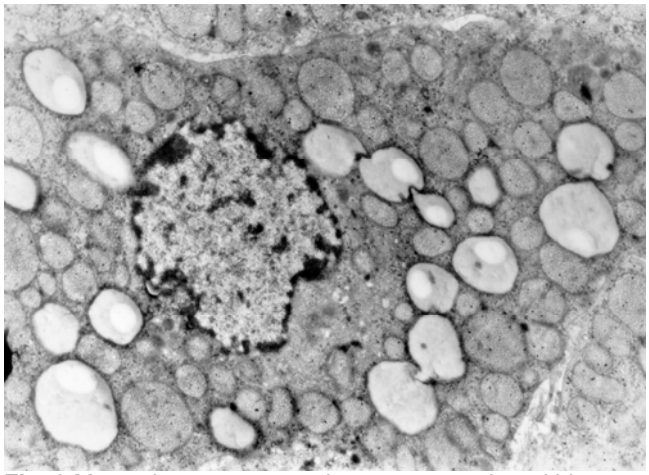

Fig. 3 Many alterate structure hormone granules within adrenal cortex fasciculata zone , x12.600

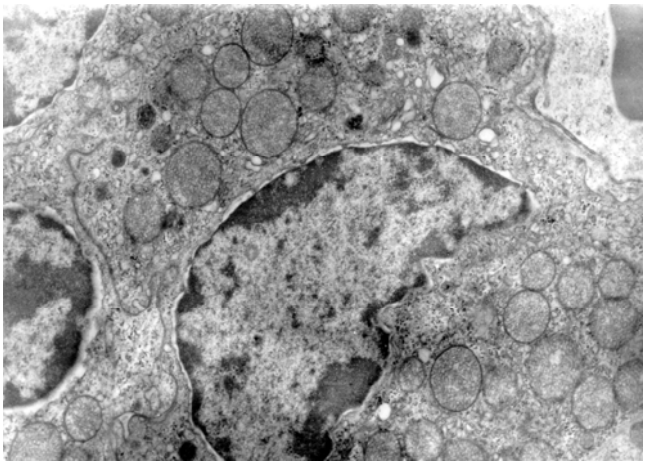

Fig. 4 Spongiocyte with irregular nucleus. Normal aspect of mitochondria, x12.600

DISCUSSIONS

Adrenal glands are organs direct involved into hypothalamus-hypophysis- adrenal axis working and into body's stress conditions adaptive reactions which play an important role in the body's immune reactions (Giurgea R, 1994; Karp et al, 2004).

Then were remarked interrelations between primary lymphoide organs for example those of thymus with adrenal glands and there was proved the presence of both of a negative feed-back between the two organs and a lot of thymus peptids can affect some adrenal cortex functions (Shigeru S et al, 2002)

After giving CFA we can noticed an easy adrenal gland hypertrophy associated with relative weight increasing of these organs. This shows that some stress phenomena became visible within animal body after performing chemotherapy. These outcome are strengthen by C vitamin and cholesterol content results

which are easy increasing in comparison with the control. These are substances involved in corticosteroid synthesis hormones and which are released in high amounts in stress conditions by inducing different poisonous substances into the body.

CFA treatment adrenal tissues changes occurred more discrete than in the case of immune system organs. Although, this thing was expected as cyclophosphamide primarily stops cellular divisions and consequently, it acts violently upon organs when cell proliferation processes are intense (eg.thymus), were cell releasing rate is higher, but it is not the case for adrenal glands (Pasca C et al, 2000). Obviously, we refer to morphological changes, those functional ones could exist in a high degree, but this can't take place morphologically.

Table 2

EVOLUTION OF SOME BIOCHEMICAL PARAMETERS DETERMINED FROM CFA TREATED WISTAR RATS ADRENAL GLANDS

PARAMETERS	CONTROL	CFA
Vit. C	**264±9,37**	**302±8,91**
mg/100 g	**(7)**	**(7)**
	-	**+14,39**
	-	**p<0,02**
Cholesterol SR	**1197±87,92**	**906±53,58**
mg%	**(7)**	**(7)**
	-	**+24,31**
	-	**p<0,02**

CONCLUSIONS

Adrenal glands, involved in body reaction to stress phenomena, after a short time since giving CFA, show a organ hypertrophy aspect with body relative increasing weight and glucocorticoids hormones intense secretion.

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