

TESTICULAR MESOTHELIOMAS IN RATS EXPOSED TO N-2-FLUORENYLACETAMIDE (FAA)

Ref

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The incidence of testicular mesotheliomas after exposure to the carcinogen N-2-fluorenylacetamide (FAA) was studied in Fischer 344 rats. The animals were fed a carcinogenic diet (containing 0.06 % FAA) for 4 weeks and then a control diet for 1 week. This schedule was carried out for 3 complete cycles (12 weeks). A smaller group of rats was treated with FAA for 1 complete cycle only (4 weeks). One group of untreated controls was also available. The surviving rats were sacrificed at 59 weeks of age. The administration of FAA for 3 complete cycles resulted in a high incidence of liver, testis and Zymbal-gland tumors. The testicular tumours were mesotheliomas and occurred in 9/25 rats. No such tumour was observed in animals treated for 1 cycle only or in untreated controls. The high incidence of testicular mesotheliomas, a rare type of tumour in this and other rat strains, suggests an association with the treatment. The present experimental model may be useful in elucidating the mechanisms of the induction of mesothelial tumours of the testis by chemical carcinogens.

In man, mesothelioma (adenomatoid tumour) of the testis and paratesticular tissue is a well-recognized entity (6, 7): its mesothelial origin has been confirmed by histochemical, ultrastructural and immunohistological observations (1, 3, 13). The spontaneous development of testicular mesotheliomas in rats is rare (4, 11). The chemical induction of testicular mesotheliomas in different strains of rats has been reported by Morris et al. (10), Greenblatt and Lijinsky (8), and Berman and Rice (2).

The present paper describes the occurrence of testicular mesotheliomas in rats fed the carcinogen FAA. This experimental model may be useful in elucidating the mechanisms involved in the production of such tumours.

Material and methods

A group of 25 male Fischer 344 rats, 4 weeks old, was fed a carcinogenic diet containing 0.06 %

FAA for 3 weeks and then a control diet for 1 week. This schedule was carried out for 3 complete cycles (12 weeks). A group of 5 rats was treated with FAA for 1 complete cycle only (4 weeks). A group of 27 untreated controls was also available. After cessation of treatment, the rats were fed control diet only. All rats were checked twice daily and weighed twice a month; the surviving rats were sacrificed at 59 weeks of age. Complete autopsies were performed on all animals, and haematoxylin and eosin-stained sections from all major organs, including both testes were prepared for histological examination.

N-2-Fluorenylacetamide (FAA) was obtained from Aldrich Chemical Co., Gillingham, Dorset, U.K.; 2.4 g were dispensed, in a fume hood, into 250-ml stoppered flasks, and 80 ml arachis oil (antioxidant-free) were added and stirred with a magnetic stirrer until a uniform suspension was obtained. All procedures were carried out on trays; and all apparatus used was decontaminated with bleach, followed by Decon, and rinsed over-

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Fig. 1 - Testicular and epididymal mesothelioma.



Fig. 2 - Low-power view of a papillary mesothelioma arising in the parietal layer of the tunica vaginalis of the testis.

night, before being washed conventionally. The FAA suspension was added to 4 kg powdered MRC 41 B diet and blended, in a fume hood, in a stoppered Hobart mixer. The mixture yielded a diet containing 0.06 % FAA and 2 % arachis oil. These diets were prepared on a weekly basis. The average diet consumption was measured twice weekly. All personnel in the special treatment rooms wore disposable aprons, caps, breathing masks and overshoes.

Results

At 59 weeks of age, when the experiment was terminated, only 3/25 of the rats treated with 3 cycles of FAA were still alive. In the groups treated with 1 cycle of FAA and in controls, the survival rate was 100 %. The average body weights in the group treated with 3 cycles of FAA showed a marked depression during the treatment period when compared with those of animals in the other experimental groups.

The administration of FAA for 3 complete cycles (12 weeks) resulted in a high incidence of testicular, liver and Zymbal-gland tumours.

The testicular tumours were mesotheliomas and occurred in 9/25 (36 %) of the rats: no such tumour was observed in animals treated for 1 cycle only or in untreated controls. All of the testicular mesotheliomas were seen at autopsy. Macroscopically, these tumours appeared as flat, nodular or papillary growths on the surface of the testis and/or epididymis (fig. 1). Microscopically, the tumours seemed to arise from the surface of the peritesticular mesothelium (fig. 2-4). The first testicular mesotheliomas were observed 30 weeks after end of the treatment. No metastasis from these tumours was found. No mesothelioma was seen to arise from other peritoneal or thoracic surfaces.

The liver tumours observed at autopsy were multiple nodes, ranging in diameter from 0.5 to 2 cm and more, and involving all lobes. The tumours in 24/25 of the rats were diagnosed histologically as hepatocellular carcinomas and those in 5/25 rats as cholangiocarcinomas. Extensive lung metastases were observed in 8/25 rats with hepatocellular carcinomas. These tumours were the major cause of death. No liver tumour was found in the other experimental groups.

All Zymbal-gland tumours observed were diag-

nosed as carcinomas. No endocrine organ tumour was observed in treated or control animals.

Discussion

Morris et al. (10) observed papillary mesotheliomas of the testis in 3/18 rats of the Buffalo strain fed FAA and in 2/6 controls. Greenblatt and Lijinsky (8) observed such tumours in 4/12 MRC-Wistar rats fed *N*-nitrosopyrrolidine (16 mg/kg/day for 67 weeks) and in 0/34 controls. Berman and Rice (2) obtained a high incidence of testicular mesotheliomas following the administration of a single i.p. dose (13 mg/kg bw) of methyl(acetoxymethyl)nitrosamine to male rats of three different strains: in 9/25 Fischer 344 rats, in 4/27 CD rats and in 12/26 rats of the Buffalo strain. All testicular mesotheliomas described by these authors were similar to those reported in the present study: macroscopically flat, nodular or papillary growths, usually with a histological papillary pattern, rare mitoses, and no metastases. Coleman et al. (5) in his study of spontaneous tumours in 133 Fischer 344 rats, observed 3 testicular mesotheliomas in animals dying at 18-30 months of age.

In the present study, the average latency of the testicular mesotheliomas was 51 weeks. The high incidence of this type of tumour suggest a relationship with treatment. In this and in the other reported studies, mesothelium-lined surfaces other than the testis did not develop mesothelioma (2, 8).

The formulation of hypotheses concerning the mechanism by which the testicular mesotheliomas are induced is beyond the scope of this study. A possible cause of their induction is hormonal imbalance: administration of FAA to Sprague-Dawley rats was associated with marked modifications of testicular activity, together with changes in the levels of sex steroid hormones (9). Hormonal imbalance due to neoplastic involvement of the liver both in our study and in that of Greenblatt and Lijinsky (8) could have played a role in the induction of the testicular mesotheliomas. Berman and Rice (2) suggest the possibility that methyl(acetoxymethyl)nitrosamine has a direct action on the testicular mesothelium. In man, the geographic variations in the incidence of this tumour, as well as the rising incidence observed in several countries, may indicate environmental risk factors (12). Epidemiological studies of testicular tumours in relation to specific carcinogenic exposures are needed.

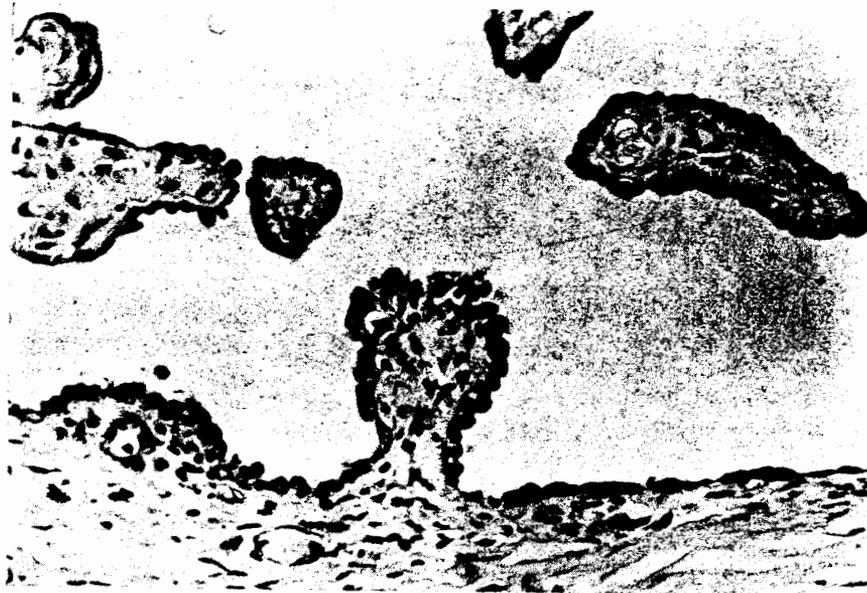


Fig. 3 - Papillary mesothelioma of testis. The flat mesothelial cells on the right grade progressively into close-packed cuboidal cells at the tip of the papillary process.

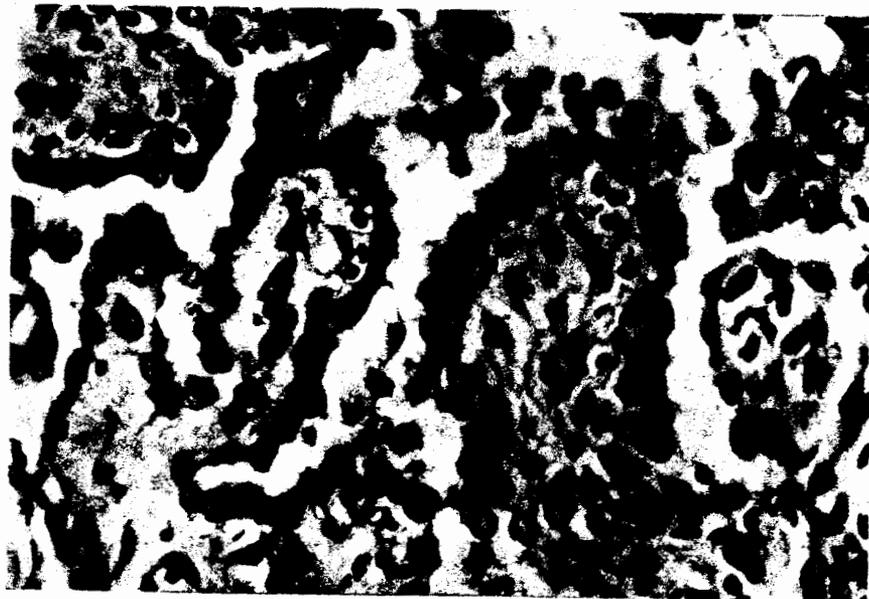


Fig. 4 - High-power view of the section shown in Fig. 2. Mesothelial cells lining inter-papillary crypts.

Mesoteliomi testicolari in ratti esposti a N-2-fluorenilacetamide (FAA)

È stata studiata l'incidenza di mesoteliomi testicolari in ratti Fischer 344 trattati con il cancerogeno N-2-fluorenilacetamide (FAA). Gli animali sono stati nutriti con una dieta contenente 0,06 % FAA per 3 settimane e in seguito con una dieta di controllo per 1 settimana. Questo programma è stato eseguito per 3 cicli completi (12 settimane). Un gruppo più piccolo di ratti è stato trattato con FAA solo per un ciclo (4 settimane), mentre un altro gruppo è stato usato come controllo non trattato. I ratti sopravvissuti

sono stati sacrificati all'età di 59 settimane. La somministrazione di FAA per 3 cicli completi ha aumentato l'incidenza dei tumori del fegato, del testicolo e della ghiandola di Zymbal. Mesoteliomi testicolari sono stati osservati in 9/25 ratti. Negli animali trattati solo con un ciclo o nei controlli non trattati non sono stati osservati tumori del genere. L'alta incidenza di mesoteliomi testicolari, tipo di tumore raro in questo o in altri ceppi di ratto, suggerisce un'associazione col trattamento. Questo modello sperimentale potrebbe essere utile per chiarire i meccanismi dell'induzione di mesoteliomi testicolari per mezzo di cancerogeni chimici.

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