Chondral Dysplasia Induced by Zirconium and Hafnium

Walter B. Shelley
Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

SUMMARY

Dysplasia of cartilage in the external ear of ICR and CBA/J mice was induced regularly by a single intradermal injection of zirconyl chloride. An identical response was seen following the local injection of hafnium oxychloride, whereas cartilaginous changes were not seen in control animals that were given similar injections of salts of aluminum, beryllium, cadmium, chromium, cobalt, and nickel.

INTRODUCTION

Zirconium has long been viewed as an innocuous trace element, without a discernible biological function (10). Its singular record for being a relatively nontoxic, well-tolerated metallic element has been marred only by the observation that zirconium salts may, under unusual clinical or experimental circumstances, produce an immune granuloma in a small percentage of people (11). Although an early study was suggestive (12), we wish now, for the first time, to report a unique, predictable, pathological effect of zirconium, namely, the production of cartilaginous dysplasia.

MATERIALS AND METHODS

Eighty female white ICR mice, 12 weeks of age, were given a single intradermal injection of one of a variety of metallic compounds. The salts used were aluminum chloride (hexahydrate), beryllium sulfate (tetrahydrate), cadmium acetate (dihydrate), chromium potassium sulfate (dodecahydrate), cobalt chloride (hexahydrate), hafnium oxychloride (octahydrate), nickel chloride (hexahydrate), and zirconyl chloride (octahydrate). Dissolved in a 0.003 M concentration in an aqueous 0.9% sodium chloride solution, each metallic salt was injected (0.02 ml) into the dorsa of the ear lobes of 10 mice that had been lightly anesthetized with ether. Two months later the animals were sacrificed, and stained serial sections of the ears were analyzed.

A similar study of 6 of the metallic salts was done on sixty 16-week-old female CBA/J agouti mice. Five months later these mice were also sacrificed for gross autopsy observation and for a serial microscopic study of the ear injection sites. Stains included hematoxylin and eosin, as well as toluidine blue (5), for visualization of the cartilaginous matrix.

RESULTS

All 20 ICR and CBA/J mice that received zirconyl chloride injections showed progressively enlarging papules at the injection sites in the ear. Grossly, the findings were not as dramatic as seen with injections of higher concentration (12) but, histologically, each mouse showed significant enchondromas, i.e., outgrowths from the cartilaginous plate. The growths were present at both 2 and 5 months, but were not found at 2 weeks in a special group of 10 CBA/J mice given injections of zirconyl chloride. All of these chondrocytic masses appeared to arise from the upper surface of the plate corresponding to the side of the ear that had been treated by injection. The excrescences were of various forms and sizes, presenting as either small hyperplastic mounds, wedge-like thickenings 4 to 6 times the width of the plate, irregular solid dysplasias, or exuberant serpentine and tongue-like extensions through the dermis (Figs. 1 to 7). The new chondrocytes, appearing to arise in thickened perichondrium, were embedded in matrix which was well vascularized. Enchondromas were not seen.

The toluidine blue stains demonstrated a strikingly metachromatic cartilaginous matrix in all of these growths (Fig. 2). Mitotic figures were present. Often there was associated fibrous tissue hyperplasia, and some tumors appeared as true fibrochondromas. There was no overgrowth of fat, and at no time did the tumors enter or penetrate the overlying epidermis.

The same findings were seen in the external ears of each of the 20 ICR and CBA/J mice that was given a single injection of hafnium oxychloride. The histological patterns were virtually identical with those seen following the intradermal injection of zirconyl chloride (Fig. 8). The remaining 100 mice, each of which was given a single injection of soluble salts of aluminum, beryllium, cadmium, chromium, cobalt, and nickel showed no abnormal gross or histological changes in either the 2- or 5-month series.

DISCUSSION

The results attest to the specific capacity of the zirconium ion and its atomic partner hafnium to produce benign cartilaginous growths. Noteworthy is the finding that under these conditions the well-known experimental metallic carcinogens (3), beryllium, cadmium, chromium, cobalt, and nickel, failed to incite any late gross or histological change. The observation that a highly acidic salt such as aluminum...
chloride was without effect supports the view that cartilaginous response is not simply a nonspecific response to chemical trauma or irritation.

The fact that only 1 injection of zirconium or hafnium in the order of 20 μg was needed to induce chondroma formation suggests a persistence of these metallic salts. We note with interest that zirconium concentrates in fatty tissue (9) and that the chondrocytes of the mouse ear contain fat (13). As yet, the precise induction period is not known, but months are required to produce a gross change. Although the response was noted in several different strains of mice, further study will be required to assess the range of responsive species, the susceptibility of the other types of cartilage, and the possibility of inducing neoplastic change in long-term, multiple-injection experiments.

This is the 1st time a pure chemical has been shown to induce chondrocyte proliferation. Up to this point, the only methods available for the experimental production of cartilage have been mechanical compression and rotation fracture (4, 8), periosteal injury (6), or the injection of cells [spinal (7), amniotic (14), or devitalized (2)]. Therefore, zirconium and hafnium injections may give us a new tool for working in the field of chondrogenesis and chondroplasia. Moreover, the finding of chondromas in each of the animals given injections of either of these 2 metallic ions alerts one to the possibility of occupational and consumer hazards. Certainly, cases of congenital chondrodystrophy deserve review from the standpoint of occult zirconium or hafnium exposure.

Finally, note should be made that, in these studies, mice have responded in an identical fashion to 2 totally distinct chemical elements, hafnium and zirconium. Apparently, the remarkable chemical and physical similarities of these "twin" elements is the basis for their defiance of easy distinction, long known in the chemical laboratory (1), and now evident in the biological system.

REFERENCES

Fig. 1. Low-power view showing irregular chondral dysplasia in CBA/J agouti mouse at site of zirconium injection 5 months previously. Disruption of normal cartilage plate is seen. H & E, × 130.

Fig. 2. Growth arising from cartilaginous plate of external ear of a mouse that was given 1 injection of zirconyl chloride 2 months previously. Toluidine blue stain shows increased amount of metachromatically stained material surrounding cells. × 260.

FEBRUARY 1973
Fig. 3. Nest of chondrocytes arising in perichondrial or fibrous tissue just above normal cartilage plate in the ear of an ICR mouse. This growth appeared at the site of a single injection of zirconium chloride (0.003 M, 0.2 ml) given 2 months previously. H & E, X 330.

Fig. 4. Note vascularity in this chondral new growth arising 2 months after zirconium injection in another mouse. H & E, X 330.
Fig. 5. Plate-like growth of cartilage extending through upper dermis of a zirconium-treated mouse. Normal ear plate cartilage with small excrescence of new chondroma is seen below. H & E, X 330.

Fig. 6. Higher magnification of inset area of Fig. 5. Note mitotic figure and abundant matrix which stained metachromatically with toluidine blue. H & E, X 800.
Fig. 7. Destruction of ear cartilage plate and dysplastic chondral growth as a result of zirconium injection. H & E, x 330.

Fig. 8. Chondral mass arising on cartilage plate in ICR mouse 2 months after the injection of 0.02 ml of 0.003 M hafnium chloride. H & E, x 330.
Chondral Dysplasia Induced by Zirconium and Hafnium

Walter B. Shelley


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/33/2/287

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.