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Late Thorotrast Injury: A Surgical Case of Non-vascularly Induced Malignancy

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A surgical case of nonvascularly-administered Thorotrast-related malignancy was reported. A 75-year-old male had suffered from a venereal disease about 55 years before the present complaint. At that time, he was injected Thorotrast to his scrotal region in an University Hospital. Although very slow enlargement of the injected region had been noticed after the treatment, the patient had never payed attention to that change for a long period. Recently, he noticed the regional condition turning to rapid enlargement with a feeling of focal tention. On surgical extirpation of the pathological tissue at Kumamoto Municipal Hospital, a tumorous proliferation was found macroscopically around the intrascrotal organs. The proliferation was confirmed, on histological examinations, to be originally a granulomatous fibrosis which can be refered to as "thorotrastoma". But, noteworthy was that parts of the fibrosis turned to malignant, sarcomatous proliferation. Therefore, the present case was considered to be that of thorotrastoma-turning malignancy, after far long-term exposure to Thorotrast. Difficulties of the precise histological classification of the malignant areas were discussed.

Key Words: Thorotrast, Pathology

Introduction

In Japan, a series of large follow-up studies of late Thorotrast injuries had been carried out by Mori, Hatakeyama et al. during 1970s and 1980s. Epidemiological, statistical and pathological results have been accumulated in their major reports[1,2,4,5,9-12]. Since additional Thorotrast cases of long survival have been continuously followed up thereafter, the total number of the cases examined and recorded has been still increasing. Recently, Mori and Hatakeyama[12] summarized the last 20 years (30-50 years after Thorotrast injection) status of Thorotrast study in Japan, comparing with that in Germany. Above authors described that the proportion of some Thorotrast-related diseases including malignant hepatic tumors, liver cirrhosis, blood diseases increased statistically during this period in comparison with their frequencies in the previous decades. Sarcoma of bone and sarcoma at injection site tended also to increase in number.

The present report deals with a male Thorotrast case at injection site which revealed a sarcomatous proliferation after long-standing fibrosis.

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Clinical History

This male patient is not a war-wounded veteran in the World War II. When he was about 20 years of age (55 years before onset of the present condition), he suffered from a venereal disease and underwent a medical treatment in an University Hospital. He stated that he was injected some fluid at scrotum region in the process of the medical treatment. Although the patient had noticed, after the treatment, very slow painless enlargement of his left scrotum during a long period, he never payed close attention to the focal change. Recently (April 1990), however, the scrotal enlargement has tended to enhance rapidly with a feeling of focal tention.

At his first consultation to Kumamoto Municipal Hospital on April 9, an uneven hard mass of a large potato size was palpated at left scrotal place together with some hydropic swelling. On admission to the Hospital on April 9, condition of the tumor was re-examined and then diagnosed as "left intrascrotal tumor".

Main laboratory data obtained from blood serum before and after the surgical operation are shown in Table 1. Blood picture showed slight leucocytosis through whole hospitalization period (April 9 to May 10), counting 10100-10900 in number. Blood pressure was always within normal value. Urinalysis showed no special change.

Table 1. Laboratory Findings

Item	Normal value	April 4	April 13	May 8
Total protein	(6.5−8.0g/dl)	7.3	6.8	6.4
Albumin	(3.5−5.3g/dl)	4.4	4.6	3.6
Total bilirubin	(0.2−1.0mg/dl)	0.2	0.7	0.2
GOT	(10−40 IU)	16	11	18
GPT	(4−35 IU)	16	12	25
Al-P	(70−350 IU)	136	102	125
Total cholesterol	(130−230mg/dl)	226	160	139
Urea N	(8−20mg/dl)	21.5	11.9	16.3
Na	(135−147mEq/l)	142	140	139
K	(3.6−5.0mEq/l)	4.5	4.5	4.0
Cl	(98−109mEq/l)	105	106	108
Ca	(8.0−10.2mg/dl)	9.1	8.6	8.4

Surgical Findings

Surgical extirpation of the tumor mass including left semicastration was performed on April 10. On macroscopical observation of the excised mass, the epididymis and the atrophic testis were confirmed to be at normal locations respectively, with a neighbouring hydrocele filling cloudy fluid.

The tumorous solid mass existed around the testis and hydrocele, occupying large portion of the intrascrotal lumen. Prominent hyalinization and frequent spotty calcification could be seen within the tumorous tissue. It showed tight adhesion wiht the overlaying skin (Fig. 1).

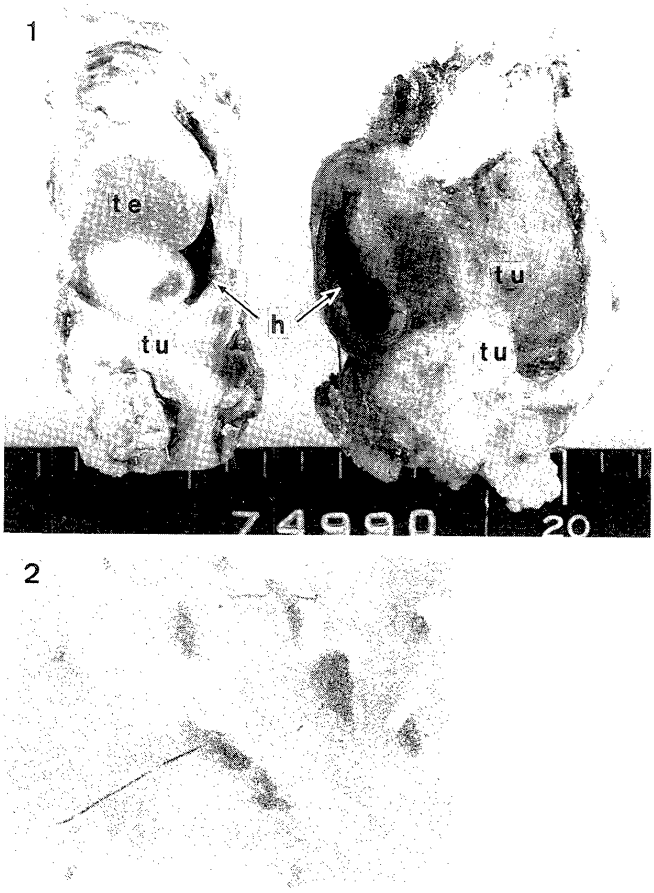


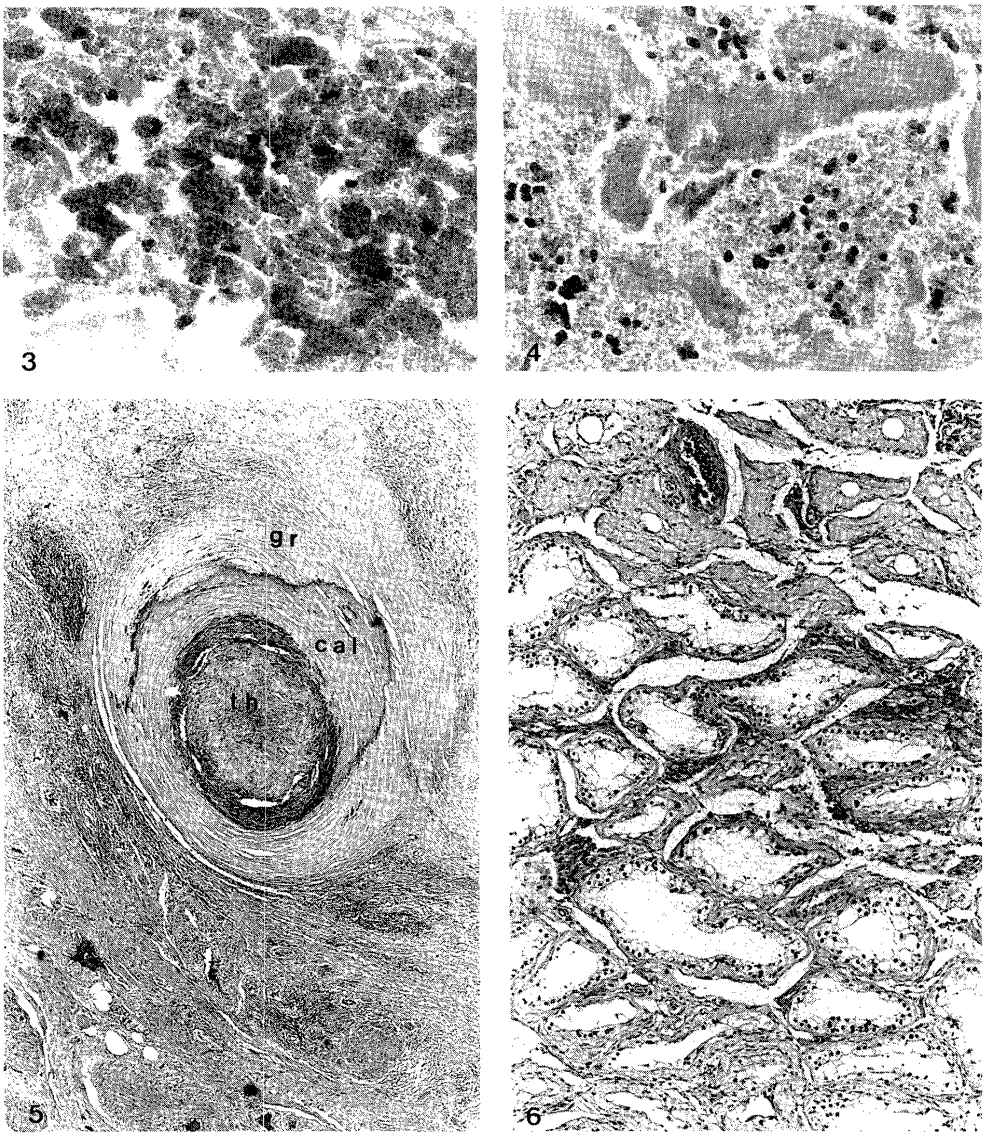
Fig. 1 Cut surface of the surgically extirpated tumor mass together with the intrascrotal organs. tu : tumorous area h : hydrocele testis te : testis

Fig. 2 Microautoradiograph for a Thorotrast-deposited tissue section. α-Tracks from Thorotrast aggregates can be seen.

Histological Findings

Histological survey of the surgically excised tissue revealed that areas of pathologic proliferation were composed mostly of marked fibrosis with scar-like or granulomatous appearances. It was conspicuous that various amounts of Thorotrast granules were deposited in these fibrous areas as aggregates or in dotted patterns (Figs. 3 & 4). Several regressive changes such as hyalinization, calcification, necrotic loosening of tissues and occasional bleeding modified the histopathology. However, both testis and epididymis as intrascrotal organs were exempted from the fibrotic involvement and appeared in rather intact profils except some senile changes (Fig. 6). All these fibrotic proliferations were regarded as to be a biological reaction of living body to foreign substance Thorotrast. This granulomatous, non-neoplastic proliferation has been known as "thorotrastoma" or "necrotic thorotrastoma" which arises in the reacting process to Thorotrast stimulus.

However, on detailed examinations of the granulomatous tissue, the authors disclosed some

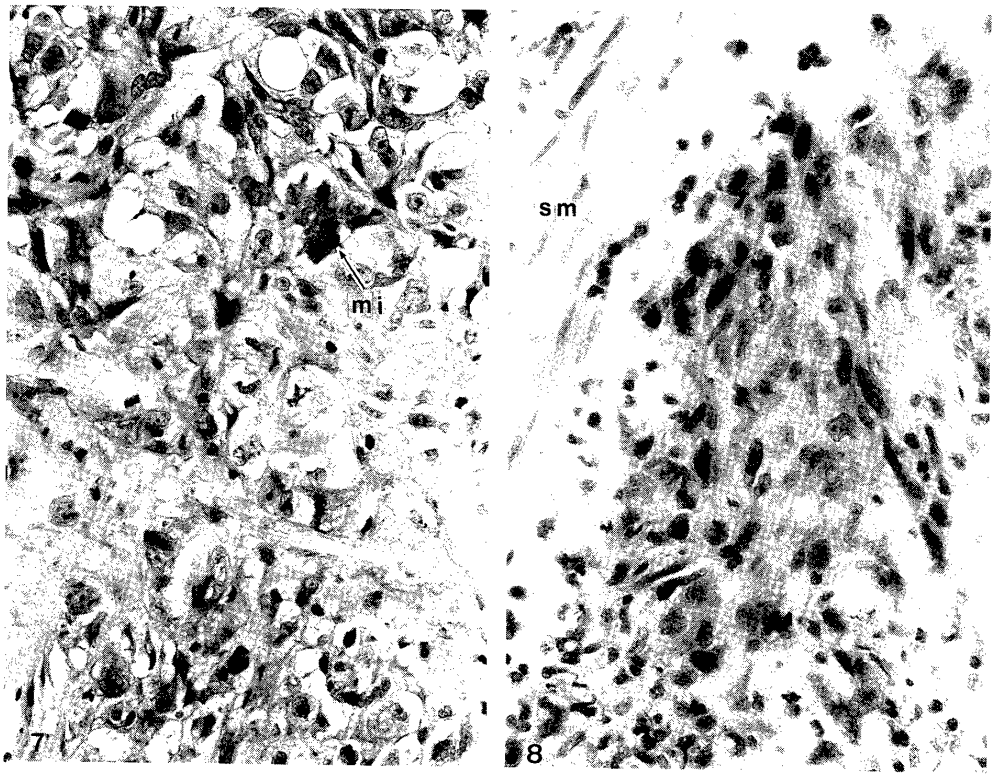


Figs. 3 & 4 Photomicrographs of Thorotrast depositition in the fibrotic areas. Thorotrast granules are deposited as aggregates (Fig. 3) or in diffusely dotted patterns (Fig. 4). Dense large particles are cell nuclei.

Fig. 5 A typical area of granulomatous fibrosis. Thorotrast deposition (th) exists in the center of the granuloma and collagenous fibers encircle the center (gr), accompanying partly calcification (cal).

Fig. 6 Testis situated near the tumorous mass. The testicular parenchyma is exempted from Thorotrast deposition as well as granulomatous involvement.

focal areas consisting of quite atypical cell groups within fibrosis or in the hydrocele-lining wall. Although these cells possessed large, atypical nuclei and wide cytoplasms in general, their histological appearances varied considerably in each area. In one atypical place, the cells were of oval nuclei and of vacuolated cytoplasms (Fig. 7), while in other portion, they appeared in profils of elongated unclei and fusiform cytoplasms (Fig. 8). Mitotic figures were occasionally encountered among these atypical cells. From above histological findings, we regarded the atypical areas as expressions of malignant cell proliferation. Since the malignant cell groups grew in the midst of



Figs. 7 & 8 Sarcomatous proliferation in the fibrous tissue. Malignant cells with atypical nuclei and vacuolated cytoplasms proliferate in random arrangement (Fig. 7), while in other part (Fig. 8) the cells appear in profiles of elongated nuclei and fusiform cytoplasms. sm : normal smooth muscle fibers adjacent to malignant cells mi : mitosis

previously existing fibrosis, the cells seemed to have developed by turning of pre-existing granulomatous tissue or, at least, under a significant influence of the long-standing marked fibrosis. However, a definite histological diagnosis of the malignant tumor was in difficulty. Because of limited extension of the malignant areas, it was hard to make more precise classification than "sarcomatous proliferation". Although the cell atypicality is much prominent, its aggressiveness is rather uncertain at present stage.

Among special stains employed to specify the malignant cell property, results from the silver impregnation technique gave us some efficient informations. Fine reticulin fibers extended inside the proliferating areas dividing single cells or small cell-groups, suggesting non-epithelial origin of the cells. Masson trichrome stain for the atypical cells appeared in cytoplasmic eosinophilia in part. However, immunohistochemical stains including desmin, cytokeratin, actin, CEA and Factor Ⅷ which were applied as means of seeking the cell origin did not reveal any reliable positive results. Thus, the malignant tumor was diagnosed histologically as "unclassifiable sarcoma" which is suspectable of leiomyosarcoma, malignant hemangioendothelioma or mesothelioma etc.

Discussion

According to the recent review on late Thorotrast injuries by Mori and Hatakeyama,[12] the chronological status of Thorotrast cases, especially in some malignant diseases, indicates considerable changes during last 20 years (30–50 years after Thorotrast administration) in contrast to that of the former 30 years. Above authors' follow-up study revealed significant increase in the propotion of hepatocellular carcinoma, liver cirrhosis, osteogenic sarcoma, blood diseases and sarcoma at injection site. Double or triple cancers also increased in number. However, among whole Thorotrast cases, neoplasms at injection site belonged always to a minority group. Because the majority of Thorotrast patients had been injected Thorotrast intravascularly for angiography or hepatolienography.

On the other hand, effects of Thorotrast as a foreign substance to living body were experimentally examined using numerous experimental animals by Wegener et al. in 1980s. Thorotrastoma in human cases as a kind of foreign body granuloma at injection site has been known from early period of Thorotrast study[9]. However, from pathological viewpoint, these fibrotic disorders are close to physiological reaction of living body to an administered foreign substance, and are basically non-neoplastic benign phenomena.

The patient presented in this report must have been injected Thorotrast through non-vascular route into his intrascrotal lumen for examination of his venereal disease, about 55 years before the recent complaint. Very slow enlargement of the injected region thereafter would indicate a mild fibrotic reaction against the continuous stimulus of Thorotrast for a long period. On histological examinations, disclosure of a sarcomatous proliferation inside the prominent fibrosis would suggest a close relationship between fibrosis and cancerization. Mori et al.[4] pointed out in their follow-up study the possibility of Thorotrastoma-turning malignant complications. Although the precise cell origin could not be clarified, we consider that our present case is able to be regarded as Thorotrastoma-transforming or Thorotrastoma-turning malignancy.

We estimated that the Thorotrast emulsion administered to this patient 55 years ago had been rather small in amount. Because of non-vascular injection and of visualizing the limited space, whole amount of Thorotrast injected would not have probably exceeded 10 ml. Accoring to the investigation data by Hatakeyama and Mori[10], amounts of Thorotrast injected for visualization of restricted spaces such as spinal cord, seminal vesicle or lacrimal gland were smaller compared with large amount use for wider spaces such as bronchography and various angiographies. The Thorotrast aggregates found on the histological sections of the present case gave us an impression that the Thorotrast deposition was not as much extensive as that observed in the hepatic hemangioendothelioma case Sasaki et al.[3] experienced in 1983.

In the whole clinical process of the present case, noteworthy was that the scar-like or granulomatous fibrosis developed finally a malignant neoplasm on basically non-neoplastic proliferation. Occurrence of a vaiety of sarcomas on the basis of thorotrastoma has been reported in literature, but their actual occurrence rate[9] is described to be less than 5%.

As it is well known, thorium (^{232}Th+^{238}Th) and its decay products once administered to a living body remain in the body for a long period, emitting α-ray at their deposited sites (biological half life 200 to 400 years). Since the patient presented here was a non-vascularly injected case, he could be exempted from wider spreading of Thorotrast through blood flow. Accordingly, both fibrosis and subsequently occurred neoplasm could be confined to the regional portion at the stage

of surgical operation.

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