Virchows Arch. A Path. Anat. and Histol. 389, 119–125 (1980)

Virchows Archiv A

Case Report

Ataxia-Telangiectasia with Renal Cell Carcinoma and Hepatoma

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Summary. This paper reports the occurrence of renal cell carcinoma, hepatoma and malignant hepatic mixed tumor in a 22-year-old male with ataxia-telangiectasia (AT). Incidence of various malignant neoplasms is high in the patients with AT. The majority of these are lymphoreticular tumors and leukemia, and epithelial tumors are rare. This report is the first case with renal cell carcinoma and the second with hepatoma. The reason for a low incidence of epithelial tumors in AT is still obscure. It is possible that as the result of abnormal aging the tumors expected in the aged will occur in longer survivors with AT.

Key words: Ataxia-telangiectasia – Renal cell carcinoma – Hepatoma – Malignant hepatic mixed tumor.

Introduction

Ataxia telangiectasia (AT), originally described by Louis-Bar in 1941, is a clinical syndrome characterized by progressive cerebellar ataxia, oculocutaneous telangiectasis and frequent sinopulmonary infections beginning in early childhood. Patients typically have manifestations of defective cellular immunity and absent or low levels of IgA among other abnormalities (McFarlin et al. 1972; Sedgwick et al. 1972).

Incidence of various malignant neoplasms is high in the patients with AT (Gatti et al. 1971; Kersey et al. 1973). The majority of these are lymphoreticular tumors and leukemia, and epithelial tumors are rare.

In this paper, a 22-year-old male patient with AT associated with renal cell carcinoma, hepatoma and malignant hepatic mixed tumor is reported and a possible reason for the occurrence of epithelial tumors in the longer survivors with AT is discussed.

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0340-1227/80/0389/0119/$01.40

Case Report

The patient was a 22-year-old Japanese male. He began to have a waddling gait at the age of three. Involuntary movements of both hands and dysarthria occurred at five. Clinical diagnosis of AT had been made at the age of eight. The major diagnostic features at that time included progressive cerebellar ataxia, telangiectasis of bulbar conjunctiva, frequent episodes of pneumonia and decrease of serum level of IgA. When he was 22 years old, he complained of chest pain, fever and dyspnoea and he died of respiratory insufficiency.

General physical examination revealed telangiectasis of bilateral bulbar conjunctiva. The hair and skin were coarse and the face was progeric. On neurologic examination there were weakness and muscle atrophy of extremities. Deep tendon reflexes were minimal in the upper extremities and absent in the lower extremities, with no pathological reflex. Cerebellar dysarthria, involuntary movement of both hands and nystagmus were seen. He required support because of waddling gait.

Serum immunoglobulin levels were as follows: IgG; 980 mg/dl, IgM; 320 mg/dl, IgA; 56 mg/dl. Lymphocyte blast transformation after phytohemagglutinin stimulation was low, with a rate of 20–30% transformation (normal control; 70–80%). Liver function tests were as follows: sGOT; 35 U/dl, sGPT; 40 U/dl, LDH; 425 U/dl and α-fetoprotein; 238 ng/dl. Au-antigen (−). An X-ray examination revealed a solitary round shadow in the right hypochondrium (Fig. 1).

Autopsy Findings

Pathological findings of AT were as follows: 1) aplasia of thymus, 2) telangiectasis of bulbar conjunctiva, cerebrum and cerebellum, 3) atrophy of cerebellum, 4) demyelinization of Goll's column of spinal cord, 5) hypoplasia of spleen, lymph nodes and lymph apparatus of intestines, 6) nucleomegaly in ectodermal (adrenal medulla), mesodermal (adrenal cortex, kidney, lymph nodes, spleen and testis) and endodermal organs (lung) (Fig. 4C), 7) atrophy of testis, 8) progeric skin, hair and face, 9) kyphoscoliosis.

Liver weighed 550 g. On cut surface, a grayish yellow lobulated nodule, $2.5 \times 2.0 \times 2.0$ cm in size, was found in the right lobe near porta hepatis (Fig. 2A). It showed slight bile staining. Microscopically the tumor was partly encapsulated by thin fibrous connective tissue. The tumor cells, with large and hyperchromatic nuclei and prominent nucleoli, proliferated in a trabecular or pseudoglandular pattern. Hyalin globules were present. This lesion was diagnosed as hepatoma, Edmondson Grade-II (Fig. 3A).

Beneath the diaphragmatic surface of the liver, there was a white round nodule, $2.0 \times 1.5 \times 1.5$ cm in size, containing bone (Fig. 2B). This lesion was considered to represent the solitory round shadow on the X-ray film. A small nodular lesion was situated beside it. Microscopically the former was composed of bone, smooth muscle cells and epithelial cell nests (Fig. 3B). The epithelial cells had large nuclei and eosinophilic cytoplasm (Fig. 3C). The stroma was rich in blood vessels, being composed of smaller tumor cells than those of the hepatoma mentioned above. The tumor cells proliferated in cords showing slight pleomorphism and no group of immature hepatic cells was seen (Fig. 3D). This lesion was considered to be a malignant hepatic mixed tumor.

In the upper polar portion of the right kidney, a small white nodule, $0.5 \times 0.5 \times 0.5$ cm in size, was found (Fig. 4A). Microscopically this lesion was well-circumscribed by thin fibrous capsule and showed papillo-tubular proliferation

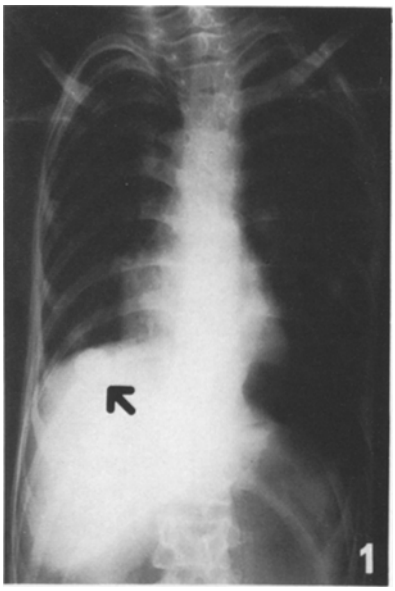

Fig. 1. A solitary round shadow (*arrow*) in the right hypochondrium

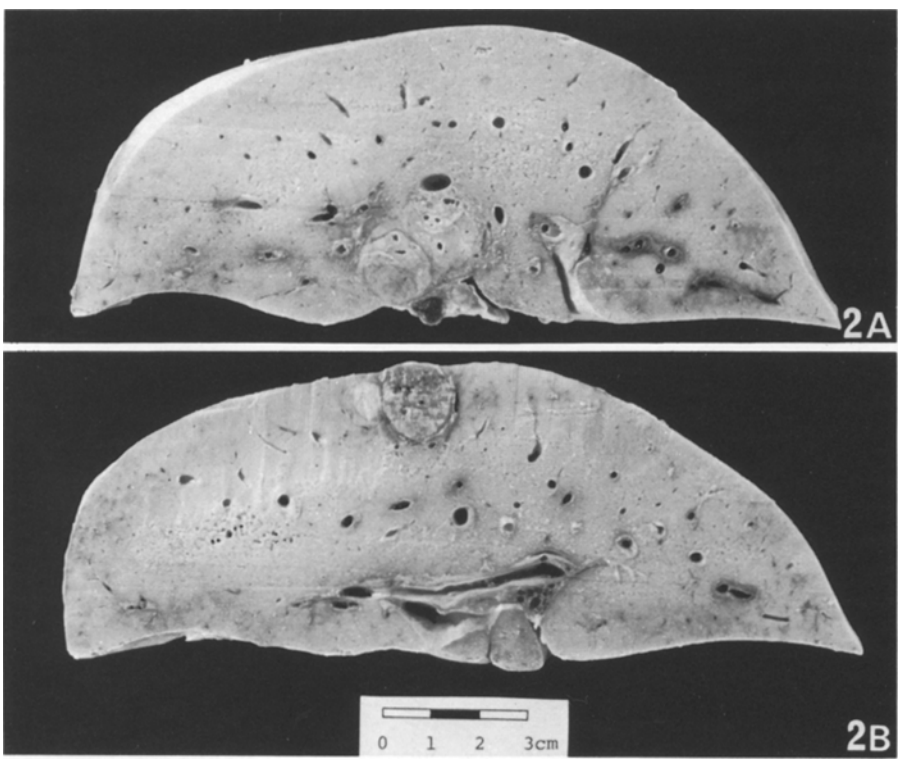

Fig. 2. A A grayish yellow nodule in the right lobe near porta hapatis. **B** There is a white round nodule containing bone and a small nodular lesion both beneath the diaphragmatic surface of the liver

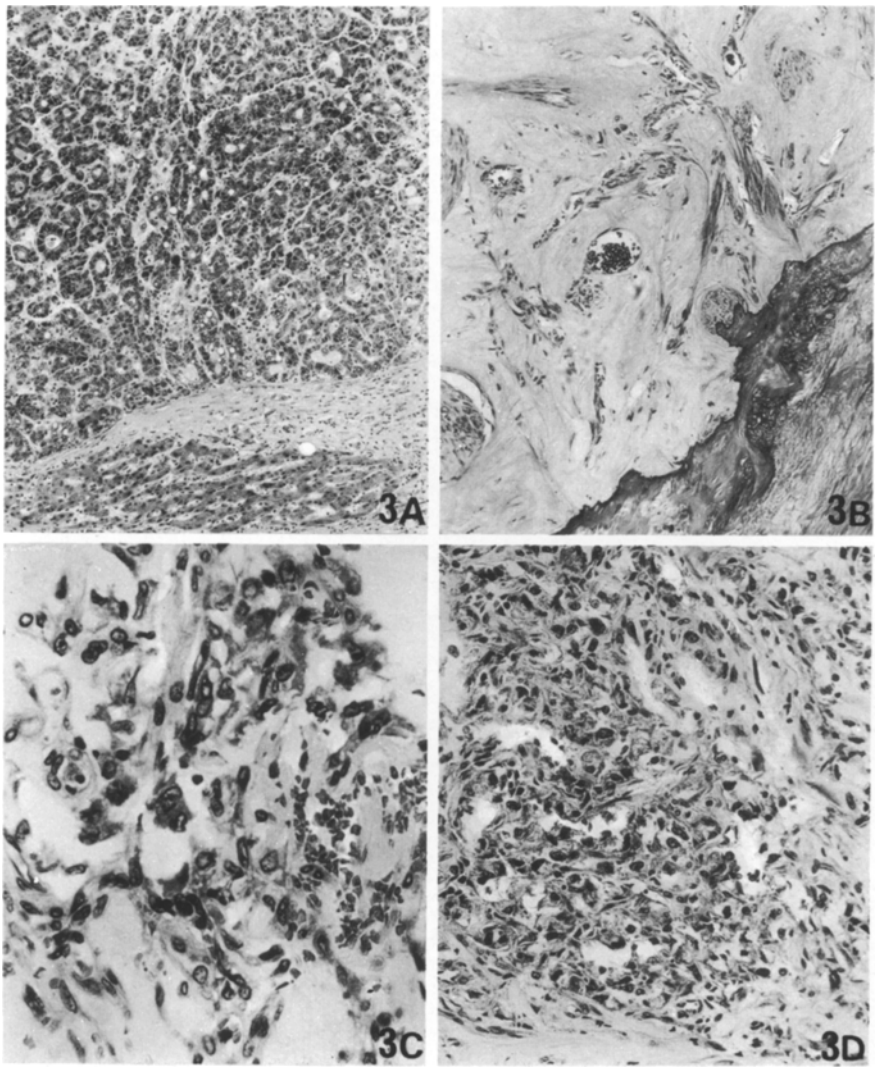

Fig. 3. A Hepatoma. Tumor cells proliferate in trabecular or pseudoglandular pattern. H&E, ×63. **B** A white round nodule is composed of bone tissue, smooth muscle cells and epithelial cell nests. H&E, ×90. **C** The epithelial cells have large nuclei and eosinophilic cytoplasm. H&E, ×350. **D** Small tumor cells showing slight pleomorphism proliferate in cords. No group of immature hepatic cells is seen. H&E, ×170

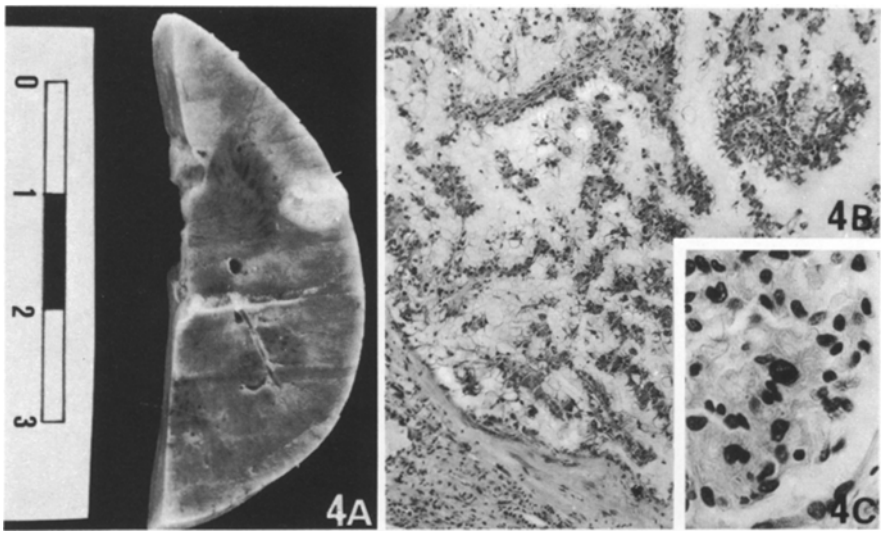

Fig. 4. A A small white nodule is found in the upper polar portion of the right kidney. **B** Renal cell carcinoma. Tumor cells with clear and vesicular cytoplasms proliferate in papillo-tubular pattern. H&E, ×63. **C** Nucleomegaly in the kidney. H&E, ×350

of pleomorphic tumor cells with clear and vesicular cytoplasm containing PAS-positive and diastase resistant granules (Fig. 4B). Sudan-III staining was also positive. This lesion was diagnosed as renal cell carcinoma.

Discussion

There can be little doubt that this case represents AT. According to Gatti and Good (1971), approximately 10–15% of the patients with AT were estimated to have malignant neoplasms, but most of these were lymphoreticular tumors and leukemia, and epithelial tumors were rare. Of epithelial tumors, gastric cancer (Haerer et al. 1969; Kondo and Horikawa 1975; Watanabe et al. 1977), basal cell carcinoma (Levin et al. 1971), ovarian dysgerminoma (Goldsmith and Hart 1975) and hepatoma (Kumar et al. 1979) have been reported, but the association of renal cell carcinoma has not been reported so far.

It is thought that the occurrence of malignant neoplasms in AT is due to inability of decreased cellular immunity to reject the malignant transformed cells (Thomas 1959). The reason why the cells originated from lymphoreticular system show neoplastic change frequently compared with those of other organs is obscure.

Known cases of AT with malignant neoplasms were classified according to the age of death (Table 1), where our case with renal cell carcinoma and hepatoma is included. Fig. 5 shows the number of cases with lymphoreticular tumors and leukemia and with epithelial tumors according to the age of death.

Table 1. Malignant neoplasms in the patients with AT

Type of malignancy	Age (year)						Total
	0–5	6–10	11–15	16–20	21–25	26–	
Lymphoreticular							
Malignant lymphoma	4	8	4	1	1		18
Hodgkin's disease	1	2	1				4
Leukemia	2	5	4				11
Nervous system							
Glioma				1			1
Medulloblastoma			1				1
Epithelial							
Basal cell carcinoma					1		1
Gastric cancer			1	1	3		5
Ovarian dysgerminoma				1			1
Hepatoma					2		2
Renal cell carcinoma					1		1
Total	7	15	11	4	8	0	45

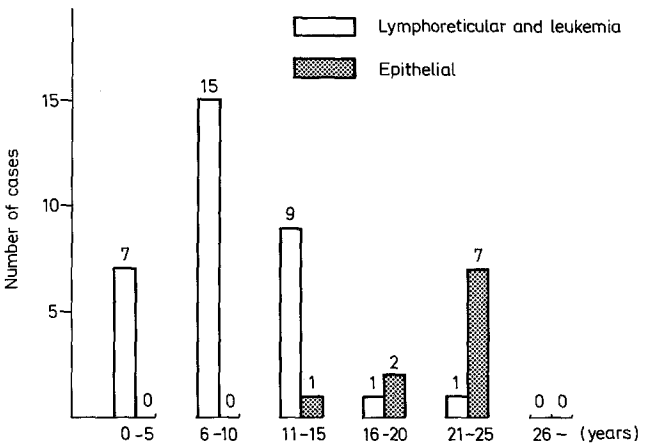

Fig. 5. Age distribution of cases with lymphoreticular tumors and leukemia and with epithelial tumors in the patients with AT

All the cases with leukemia and most of those with lymphoreticular tumors were under the age of fifteen, and most of those with epithelial tumors were beyond sixteen. In AT, the lymphoreticular tumors and leukemia tend to occur earlier than the epithelial tumors which usually develop in the adult and the aged.

The nucleomegaly in the patients with AT, which Bowden et al. (1963) pointed out in the hypophysis for the first time, is noted in a variety of organs systematically. Kamoshita (1973) suggested that the nucleomegaly might be due to precocious aging, because it was found in the patients with progeria,

and the skin, hair and face of the patients with AT were similar to those with progeria. It seems that as the result of abnormal aging the tumors of the aged occur in longer survivors with AT. A low incidence of epithelial tumors may be due to the short life span in the majority of patients with AT.

Waldmann and McIntire (1972) reported high levels of α-fetoprotein in the patients with AT. It is of interest that none of the patients reported was pregnant or had testicular, ovarian or hepatic tumors. They mentioned that the synthesis of this fetal protein of hepatic origin in the patients with AT suggested that the liver was not fully developed in these patients and that it supported the hypothesis that a primary abnormality of the patients with AT was a defect in tissue differentiation. It was obscure whether the elevation of α-fetoprotein in our case was due to abnormality of development of the liver or the hepatoma itself.

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Accepted July 8, 1980