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CHAPTER 67

Diverse Cancers in Genetic Disorders: Case Series Compared

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The arrays of neoplasms in six genetic syndromes differ from one another, although there is some overlap. Soft tissue sarcomas and osteosarcomas occur excessively, but not in the same ratio in Werner (premature aging) syndrome (WS), Li-Fraumeni syndrome (LFS), and Rothmund-Thomson syndrome. Excesses of leukemia of dissimilar types occur in the chromosome instability syndrome: Bloom syndrome (BS), Fanconi anemia (FA), and ataxia-telangiectasia (A-T). BS and A-T have excesses of lymphoma. In adulthood, carcinomas occur excessively in BS and FA. Japanese with WS have marked increases in three rare cancers; persons with LFS are predisposed to four others under the age of 45. Laboratory research should provide explanations for such peculiarities of cancer occurrence in genetic disorders.

INTRODUCTION

This report arises primarily from small-group workshops held under the U.S.–Japan Cooperative Cancer Research Program. Haruo Sugano and I have been associated with the program since its inception in 1974 and have overseen or organized 32 binational workshops since 1981 (1). Some concerned cancer genetics (clinical and epidemiological aspects) well before advances in molecular biology made the subject a hot topic. Holding the workshops over 17 years enabled the development of ideas from one workshop to another, stimulating innovative thinking.

Recently, our attention has focused on cancers in genetic syndromes—how the spectrum differs in each, overlapping in some syndromes and completely different

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in others. We compared cancer in three chromosome instability syndromes (2–4) with Werner Syndrome (WS), or adult progeria (5); Li-Fraumeni syndrome (LFS) (6); and Rothmund-Thomson syndrome (RTS) (Y. Ishikawa, unpublished observations). The cancers occur mainly under 45 years of age in all syndromes, except for WS in which they occurred at 25–64 years. The life span in all these syndromes is on average under age 50 years. The case series for Fanconi anemia (FA), WS, and RTS were initiated as a result of earlier workshops.

The six syndromes differ markedly in their congenital malformations, among other disorders. The main features of Bloom syndrome are very short stature, sun-sensitive rash of the face, frequently low IgA, IgG, and IgM, chromosome instability and with an excess of sister chromosome exchanges (2). Children with FA have short stature, pancytopenia, often hypoplastic thumbs, areas of brown skin pigmentation, and chromosome instability of lymphocytes in culture; 20% are mentally retarded (3). Children with ataxia-telangiectasia (A-T) have a staggering gait and telangiectasia of the bulbar conjunctivae at about 6 years of age. They have chromosome instability in culture and immunodeficiency (usually IgE and IgA and at times IgG and IgM) (4).

In WS, premature aging becomes apparent at about 25 years of age, with greying of the hair, onset of cataracts, skin changes sometimes resembling scleroderma, arteriosclerosis, and diabetes mellitus. Li-Fraumeni syndrome has no malformations and is recognizable only by family clustering of several of the six specific cancers that occur excessively under age 45 (6) (Table 67.1). In Rothmund-Thomson syndrome (*poikiloderma congenitale*), severe plaques of edema and erythema typically develop on the face at 3 months of age, and extend to the skin elsewhere, followed often by premature greying, cataracts and defective dentition (7). Except for LFS, the syndromes are clinically autosomal recessive traits and have growth retardation and hypogonadism.

Comparison of cancers by cell type in the six syndromes is shown in Table 67.1. It will be noted that soft tissue sarcoma (STS) and osteosarcoma (OS) occurred only in WS, LFS, and RTS. There is no excess of these cancers in the chromosome instability syndromes. STS and OS have embryologic origins in common, so the excess of the two together is not surprising. The ratio of STS to OS is not consistent, however, being greatest in WS and least in RTS, in which cases of OS far outnumber STS—an interesting puzzle.

Some rare cancers are markedly excessive in a particular syndrome. Acral lentiginous melanoma (ALM), one of the rarest forms of melanoma (it occurs on the palms, soles and mucosa) has about the same incidence in whites, blacks and Japanese, 0.16 per 100,000 annually. But in Japanese with WS, 20 cases were observed among an estimated 5000 people with the syndrome in a 20-year interval. Virtually no cases were expected at the rate for ALM in the general Japanese population. No excess of ALM was observed in Caucasians with WS, possibly because of a difference in genotype (8).

An excess of benign meningioma was observed in both Japanese and Caucasians with WS. Usually 25% of intracranial tumors are meningiomas, as contrasted with

TABLE 67.1. Cancer and MDS (%) in Chromosome Instability Syndromes Versus WS, LFS and RTS[a]

Neoplasm	BS	FA	AT	WS[b]	LFS	RTS
Soft tissue sarcoma				*17.2*	*23.9*	*12.0*
Osteosarcoma	2.3			*6.7*	*14.5*	*57.6*
Bone, other		0.6			4.3	
Acral melanoma				*14.9*		
Meningioma				*0.7*[c]		
Thyroid carcinoma				*15.7*	0.9	
Breast	8.1	1.7	1.0	4.5	*23.9*	
Brain	1.2	2.2	2.9	0.7[d]	*12.0*	
Adrenocortical carcinoma					*3.3*	
MDS		*13.8*		*3.0*		3.0
ANLL	*17.4*	*40.3*		*6.0*	1.7	
ALL	*7.0*	1.7	*19.0*		*4.3*	
Leukemia, other		4.4	2.9		0.9	
Non-Hodgkin lymphoma	*20.9*	0.6	*45.7*		1.7	
Hodgkin's disease	2.3		*11.4*			
Gastrointestinal	*15.1*	*9.4*	7.6	6.0	1.7	3.0
Tongue[e]	*4.7*	*3.9*				
Gynecologic	3.5	4.4	2.9	3.0	1.7	
Urogenital				3.7	0.9	
Liver		*10.5*[f]	*1.9*	3.7		
Cholangiocarcinoma				*3.0*		
Skin	*10.5*	2.2	2.9	2.2		*24.2*
Lung	1.2	1.1		0.7	1.7	
Other	5.8	3.3	1.9	6.0	2.6	
Total	86	181	105	134	117	33
Age	<46	<48	<30	25–64	<45	<56

ANLL, acute nonlymphocytic leukemia; ALL, acute lymphocytic leukemia; AT, ataxia-telangiectasia; BS, Bloom syndrome; FA, Fanconi anemia; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic; LFS, Li-Fraumeni syndrome; MDS, myelodysplastic syndrome; XP, xeroderma pigmentosum; WS, Werner syndrome; RTS, Rothmund-Thomson syndrome.

[a]Italics indicate high frequencies.

[b]Japanese cases.

[c]Fifteen benign excluded.

[d]Two benign excluded.

[e]Four posterior tongue in BS; 10 in FA. Also excess at tip of tongue in XP.

[f]Eighteen malignant plus 18 benign; 2 malignant had no androgen therapy.

84% in Japanese with WS. The excess of intracranial tumors in LFS were of neural cell type.

In the chromosome instability syndromes (BS, FA, and A-T), the predominant neoplasms are leukemia and non-Hodgkin lymphoma (NHL). WS had a smaller excess of leukemia (acute non-lymphocytic [ANLL]), the main category of leukemia

TABLE 67.2. Main Neoplasms in Genetic Syndromes

Syndrome	Neoplasms	Cases %	Cases n
BS	ANLL, NHL, GI, tongue, skin	59	86
FA	MDS, ANLL, GI, tongue, liver	78	181
A-T	ALL, NHL, HD, GI	84	105
WS	STS, OS, ANLL, acral, meningioma, GI, biliary	55	134
LFS	STS, OS, breast, brain, ACC	78	117
RTS	STS, OS, skin (nonmelanoma)	94	33

See Table 67.1 and text for definitions.

in FA. (Both FA and WS predisposed to myelodysplastic syndrome, a precursor of ANLL, not seen in BS.) In FA 40.3% of cancers were ANLL, as compared with 17.4% in BS. In A-T, the leukemias were of a different cell type—acute lymphocytic (ALL), which is unlike ANLL both cytogenetically and epidemiologically.

Non-Hodgkin lymphoma accounted for 45.7% of cancers in A-T and 20.9% in BS. In addition, 11.4% of cancers in A-T were Hodgkin's disease. In the chromosome instability syndromes, hematopoietic cancers accounted for 62% of all cancer, as compared with 7% in WS, LFS, and RTS, combined.

The most common cancer in LFS was carcinoma of the breast (23.9% of all cancers under age 45). It was not linked to a high frequency of ovarian cancer. Gastrointestinal carcinoma accounted for 15.1% of cancers in BS. There was a possible excess of gastric cancer in particular in A-T and WS. Oddly, carcinoma of the *base* of the tongue occurred in BS and WS (four cases each). Carcinoma of the *tip* of the tongue is seen in xeroderma pigmentosum (9).

Of all cancers in FA, 10.5% were hepatocellular carcinoma, which occurred after treatment with anabolic androgenic steroids. Thus, the treatment combined with the genetic disorder led to hepatic neoplasia, either benign or malignant. Biliary-tract cancer occurred in four Japanese with WS.

In WS thyroid carcinoma accounted for 15.7% of cancers in Japanese, but no such frequency was seen in Caucasians with the syndrome, possibly because of a difference in genotype (8). Four persons with LFS had adrenocortical carcinoma in childhood, a very rare cancer. Tsunematsu and associates (10) have shown that this tumor can be used as sentinel to the diagnosis of families with LFS.

In the U.S. population older than 20 years of age, the ratio of carcinoma to other forms of cancer (ie, nonepithelial cancer) is 10:1 (12). In WS the ratio is 1:1. In BS and FA cancers are mainly nonepithelial under age 20 years, and epithelial above this age, as in the general population.

The percentage of neoplasms of the main cell types in each of the six syndromes is shown in Table 67.2. The tumors listed account for 55–94% of all cancers in these syndromes. Note the overlap of hematological cell types in the chromosome instability syndromes (top three lines) and of STS and OS in the bottom three lines.

These convergences and divergences of cancer type, and the occurrence of se-

lected neoplasms in certain syndromes, are puzzles whose solutions will advance understanding of cancer biology and normal growth.

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