Oncogenesis in patients with congenital heart disease: A possible role of the neural crest

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ABSTRACT

Patients with congenital heart disease (CHD) seem to have a higher risk for specific malignancies. We hypothesize a pathogenetic link between particular congenital heart defects and cancer originating from specific cellular lineages. We report a series of patients, followed in two high-volume referral centers, with CHD involving neural crest-derived structures who developed cancer later in life. Fourteen patients (five female) developed neoplasia with a cellular origin embryologically linked to the neural crest between 2010 and 2020. If confirmed on larger datasets, this observation might support the hypothesis of common embryogenetic pathway suggesting tailored surveillance of a specific subset of patients.

Keywords: Cancer, congenital heart disease, neural crest, oncogenesis

INTRODUCTION

Various cancers account for about 7% of total mortality among adult patients with congenital heart disease (ACHD).[1] This finding, which is in line with cancer-related mortality in the general population, may be explained by the increasing number of patients with congenital heart disease (CHD) reaching adulthood. However, the recognition of a higher incidence of cancer also in the pediatric age group has led researchers to look for additional pathophysiological hypotheses bringing up the role of genetic predisposition, radiation exposure, and possible effect of chronic hypoxia.[2,3] The possible link between chronic hypoxia exposure and particular neoplasms, such as pheochromocytoma and paraganglioma, has been highlighted by some anecdotal reports since the early 60s and more recently by a larger contemporary series.[4,5] It has been pointed out that some kinds of neoplasias such as pheochromocytoma, paraganglioma, and thyroid carcinoma occur more frequently in ACHD patients. All these neoplasia share a common origin from cells of the neural crest.[6,7]

On the other hand, there is growing evidence about the role of neural crest cell migration in cardiac septation[8] and the correct development of particular heart segments such as the outflow tracts and aortic arch.[9,10] Animal experiment has suggested that complete or total ablation of the neural crests result in a wide range of conotruncal and arch congenital anomalies such as tetralogy of Fallot, truncus arteriosus, aortic coarctation, and aortic arch interruption.[11]

Based on this background, an etiopathogenetic link between specific tumors and some categories of CHD can

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be hypothesized. We report a series of patients with CHD involving neural crest-derived structures who developed cancer, looking for a possible common embryogenetic origin.

METHODS

Medical records of CHD patients followed in two centers between 2010 and 2020 were reviewed. Medical records of patients with a cancer diagnosis were scrutinized looking for a possible ontogenetic cellular match between the congenital defect and the neoplasia. Since some neoplasms, such as melanoma, have also a strict association with environmental factors and aging, we excluded patients who had developed cancer after 50 years of age.

RESULTS

Fourteen patients (five females) out of 48,860 (0.028%) congenital patients included in the combined database developed a neoplasia typically originating from neural crest cells: five cutaneous melanomas, three neuroblastomas, one thyroid medullary carcinoma, one pituitary adenoma, one meningioma, pheochromocytoma, and one pinealoblastoma. Melanomas occurred on the skin of the back in two patients, on the leg in two patients, and on the pectoral area in one patient. These patients had a congenital lesion involving the neural crest migration defect: septation and conotruncal defects, great vessel malposition, left outflow tract, and aortic arch development anomalies. One case displayed multiple in-series left heart obstruction and hypoplastic left ventricle. The median age at the last follow-up was 38 years (13–53), whereas the age at the time of cancer diagnosis was 25 years (18–40) [Table 1].

Three patients had undergone more than one operation. The median number of cardiac catheterization that the patients had undergone in the past two decades was one (maximum four). Three patients displayed desaturation at the time of cancer diagnosis with saturations ranging between 80% and 91%. None of the patients had syndromic conditions or comorbidities associated with immunodeficiency.

DISCUSSION

In this retrospective study, we found a nonnegligible prevalence of unusual neoplasia with common cellular origin from the neural crest. In particular, the prevalence of neuroblastoma in our cohort was significantly higher as compared to the one expected in the general population (6/100.000 vs. 6–10/million).[12] All these patients had a typical congenital defect involving a heart segment whose development

Table 1: Demographic and clinical features of patients

	Gender	Age (years)	Anatomy	Surgery	Age repair/ palliation*	SO_2 (%)	Surgery (*n*)	CT (*n*)	Catheterization (*n*)	Type of neoplasia	Age at neoplasia diagnosis (years)
1	Female	25	DORV	Complete repair	4 months	97	1	0	1	Medullary Thyroid cancer	25
2	Male	38	PA/VSD	Complete repair	8 months	98	1	0	2	Meningioma	36
3	Male	20	COA	Complete repair	10 days	98	1	0	0	Cutaneous melanoma	18
4	Male	50	Subaortic stenosis	Complete repair	24 months	97	1	0	0	Pituitary adenoma	40
5	Male	24	DORV + TGA + remote VSD	Fontan (TCPC)	5 years	91	3	1	3	Pheochromocytoma	22
6	Female	51	ASD	ASD closure transcath	38 years	98	0	0	1	Pheochromocytoma	41
7	female	6	VSD/subvalvular stenosis	VSD closure	6 months	98	1	0	0	Neuroblastoma	0.6
8	Male	32	Single ventricle/TGA	Glenn palliation	6 months	88	2	1	4	Neuroblastoma	0.5
9	Male	1	ASD	None		98	0	0	0	Neuroblastoma	0.5
10	Male	54	ASD	ASD closure transcatheter	50 years	99	0	0	1	Cutaneous melanoma	48
11	Female	56	VSD	VSD closure transcatheter	52 years	98	0	0	1	Cutaneous melanoma	47
12	Female	58	TOF	Complete repair	6 months	98	2	0	2	Cutaneous melanoma	34
13	Male	48	TOF	Complete repair	7 months	98	4	2	3	Cutaneous melanoma	22
14	Male	10	HLHC	Glenn palliation	3 months	80	2	1	2	Pinealoblastoma	8

*Age at repair or last palliation. ASD: Atrial septal defect, VSD: Ventricular septal defect, DORV: Double outlet right ventricle, TOF: Tetralogy of Fallot, PA: Pulmonary atresia, TGA: Transposition of great arteries, CT: Computerized tomography, COA: Coarctation of the aorta, TCPC: Total cavopulmonary connection, HLHC: Hypoplastic left heart complex

depends on the proper migration of neural crest cells. Association between thyroid cancer and conotruncal CHD has been anecdotally reported alluding to a possible embryogenetic link, although this association has never been systematically reported in larger series so far.[13]

Chronic hypoxia has been advanced as an alternative hypothesis to explain the occurrence of particular neoplasms such as pheochromocytoma and paraganglioma.[5] However, only two patients of this series had a history of persistent cyanosis supporting the rationale. Furthermore, all patients had undergone a maximum of four diagnostic catheterizations in the past two decades; therefore, we can presume a limited X-ray exposure and a not significant pathogenetic role. It has to be recognized that oncogenesis is a multifactorial process and requires multiple genetic hits; therefore, the magnitude of the association may be extremely variable in different population samples. It has to be observed that CHDs included in our series display a very heterogeneous spectrum of anatomies, ranging from complex to simple. This is consistent with recent data based on animal models suggesting a variable role of a cluster of genes that control neural crest migration, which in turn orchestrates proper development of the cardiac tube, including septation.[14]

We acknowledge that this paper has several limitations. First, the small number of patients does not allow for adjustment for other risk factors. Aging and environmental agents are important etiologic factors for some of the neoplasia considered, such as melanoma. In all patients included in our series, melanoma occurred in the body regions different from the face skin, however, we cannot exclude the role of cumulative sun exposure. Furthermore, we were not able to retrieve exact X-ray exposure data so its causative role cannot be quantified. Most importantly, our hypothesis is based purely on clinical observation and, therefore, largely speculative. However, the recognition of a specific cluster of rare neoplasia in patients with congenital defects with common embryogenetic characteristics may represent the theoretical background for mechanistic molecular research.

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Conflicts of interest

There are no conflicts of interest.

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