Syndrome-Associated Tumors by Organ System

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Abstract

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Certain tumors suggest the possibility of a patient harboring a genetic syndrome, particularly in children. Syndrome-associated tumors of the gastrointestinal tract, genitourinary tract, gynecologic tract, heart, lungs, brain, eye, endocrine organs, and hematopoietic system will be briefly discussed.

Introduction

Malignant tumors are relatively uncommon in children and represent approximately 1% of all cancer cases.¹ As a result, the diagnosis of malignancy in a child often raises the possibility of whether an inherited genetic syndrome played a role. It is unclear how many pediatric cancers arise in the setting of such syndromes, but it may be as high as one-third of cases.²

This article contains a review of childhood tumors (both benign and malignant) that may occur secondary to a genetic syndrome. Included are lesions of the gastrointestinal tract, genitourinary tract, gynecologic tract, heart, lungs, brain, eye, endocrine organs, and hematopoietic system. Many of the genetic conditions discussed herein, while not strictly pediatric syndromes, have been reported to cause cancer in young adults in their third or fourth decade, suggesting the possibility that they could lead to cancer in pediatric patients.

Esophagus

Esophageal carcinoma is exceedingly rare in children.³ The main risk factors for esophageal adenocarcinoma are tobacco and alcohol use, and the main risk factor for esophageal adenocarcinoma is a longstanding reflux disease complicated by Barrett esophagus (intestinal metaplasia)⁴; neither of these risk factors routinely affects the pediatric population, though some cases of Barrett esophagus may be familial.⁵ At least two syndromes—Fanconi anemia and tylosis—are

usually diagnosed in childhood and increase the risk of esophageal cancer, though the malignancy typically presents in adulthood.

Fanconi anemia is an autosomal recessive syndrome associated with numerous genes involved in deoxyribonucleic acid repair. Patients may display numerous congenital defects and experience progressive bone marrow failure. The most common malignancy affecting these patients is acute myelogenous leukemia, though they have a markedly increased risk for squamous cell carcinoma of the esophagus in adulthood.^{6,7}

Tylosis, also known as palmoplantar keratoderma, results from a mutation in the *TOC* gene and causes hyperkeratosis of the palms and soles. It has been linked to esophageal squamous cell carcinoma in a limited number of families, a phenomenon termed Howel–Evans syndrome.⁸ This typically occurs in later adulthood, but has been reported as young as age 29 in two separate patients.^{9,10}

Stomach

As with the esophagus, cancer of the stomach is exceedingly rare in children.¹¹ Several genetic syndromes increase the risk of development of gastric cancer, including Cowden syndrome, familial adenomatous polyposis, hereditary breast and ovarian cancer (i.e., *BRCA1* or *BRCA2* mutation), juvenile polyposis syndrome, Li–Fraumeni syndrome, Lynch syndrome, *MUTYH*-associated polyposis, and Peutz–Jeghers syndrome.¹² However, reports of gastric carcinoma arising in the

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pediatric population due to these syndromes are extremely rare. In some cases, this may be due to unusual mutational variants leading to early onset of malignancy, such as in a reported case of a 14-year-old patient with gastric adenocarcinoma and a rare *TP53* mutation causing Li–Fraumeni syndrome.¹³ Relatively young adults with syndrome-associated gastric carcinoma include a 27-year-old patient with Lynch syndrome,¹⁴ a 27-year-old patient with a *BRCA2* mutation,¹⁵ a 32-year-old patient with juvenile polyposis syndrome,¹⁶ and a 37-year-old woman with Gardner syndrome (a variant of familial adenomatous polyposis).¹⁷

Another unique syndrome that gives rise to gastric carcinoma is familial diffuse gastric cancer syndrome. This condition stems from a mutation in the *CDH1* gene and carries an approximately 40 to 63% lifetime risk of gastric cancer, which has been reported in patients as young as 14 years.^{18,19} Those affected typically develop multiple small signet ring cell adenocarcinomas of the stomach (►Fig. 1). Total gastrectomy is considered the optimal risk-reducing measure,²⁰ though surveillance endoscopy can also play a role if needed.²¹ Families with a strong history of diffuse gastric cancer that lack *CDH1* mutations may instead harbor *MAP3K6* mutations.²²

Familial mutations in succinate dehydrogenase genes have been relatively recently described and appear to play a role in hereditary paraganglioma–pheochromocytoma syndrome and Carney–Stratakis syndrome.^{23,24} Succinate dehydrogenase-deficient gastrointestinal stromal tumors (GISTs) appear to account for a fair proportion of GISTs of the stomach in the pediatric population, though they can arise outside the context of a germline mutation.^{25,26} Pediatric GISTs have also been described in Carney triad (see section “Lung”).

Small and Large Intestine

Intestinal carcinoma is rare in children, though perhaps less so than esophageal and gastric carcinoma. Studies have shown that colorectal carcinoma in pediatric patients has a poor prognosis, likely due to advanced stage at presentation.^{27–30} Some, but not all, cases have been linked to an inherited syndrome. Most syndrome-associated intestinal tumors occur due to polyposis syndromes.³¹ The most common of these is familial adenomatous polyposis, which is discussed elsewhere in this issue. A brief summary of other polyposis syndromes follows.

Juvenile polyposis syndrome, which primarily results from mutations in either *SMAD4* or *BMPRIA*, is a hamartomatous polyp syndrome that affects the lower and (as mentioned above) upper gastrointestinal tract.³² Patients develop multiple juvenile polyps that are at risk of malignant transformation; overall, the lifetime risk for development of colorectal carcinoma is nearly 40%.³³ By definition, patients must have more than five colorectal juvenile polyps, multiple juvenile polyps throughout the gastrointestinal tract, or any juvenile polyps along with a family history of the syndrome.³⁴ The polyps are microscopically distinct and do not resemble tubular adenomas, from which most sporadic intestinal carcinomas arise. While the polyps occur in childhood, ma-

lignancy typically does not arise before the fourth decade of life.³³

Peutz–Jeghers syndrome is also a hamartomatous syndrome that gives rise to polyps throughout the gastrointestinal tract, as well as mucocutaneous pigmentation. It is caused by *STK11* mutations and results in polyps with a distinctive morphology, including arborizing bands of smooth muscle.³² It is currently believed that most, if not all, Peutz–Jeghers polyps occur in the setting of the syndrome.³⁵ The polyps can harbor dysplastic change and progress to malignancy (►Fig. 2); patients are overall at a greatly increased risk for carcinoma of the gastrointestinal tract, pancreas, breast, and cervix,³⁶ and intestinal cancer can arise as young as 15 years.³⁷

The final entry in the gastrointestinal hamartomatous polyposis syndromes serves more as a category. *PTEN* hamartoma tumor syndrome encompasses four distinct clinical syndromes that result from germline *PTEN* mutations: Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome.^{32,38} These syndromes are linked by their gene of origin but otherwise have distinct clinical presentations. Cowden syndrome typically is diagnosed in young adulthood, whereas the other three syndromes are clinically evident during childhood. The majority of patients with Cowden syndrome develop various types of hamartomatous colorectal polyps,³⁹ although their risk of developing colorectal carcinoma is only approximately 9%.³² Such polyps are also considered a feature of Bannayan–Riley–Ruvalcaba syndrome, though the risk of developing malignancy is less clear in these patients. While Proteus syndrome and Proteus-like syndrome have highly variable clinical presentations and can cause several types of tumors, intestinal polyps and carcinomas are not generally considered a feature of either disease.

MUTYH-associated polyposis is somewhat similar to familial adenomatous polyposis in that it causes multiple tubular adenomas, with increased risk of developing colorectal carcinoma. However, patients with *MUTYH* mutations typically develop fewer than 100 adenomas and present in their fifth decade, making pediatric manifestations uncommon.⁴⁰ The youngest reported patient with colon cancer and a *MUTYH* mutation was 21 years old.⁴¹

In contrast, Lynch syndrome (hereditary nonpolyposis colorectal carcinoma) has been the reported or suspected cause of several pediatric colorectal carcinomas,^{42–44} including one in a 9-year-old patient.⁴⁵ This syndrome results from germline mutations in mismatch repair proteins (most commonly *MLH1*, *MSH2*, *MSH6*, or *PMS2*), which increases the odds of developing microsatellite instability and puts patients at risk for a variety of malignancies, including gastrointestinal and gynecologic carcinomas. Variants of Lynch syndrome, which are also caused by mismatch repair defects, include Muir–Torre syndrome (which causes skin manifestations)⁴⁶ and Turcot syndrome (a combination of colorectal carcinoma and brain tumors, which can also be considered a variant of familial adenomatous polyposis depending on presentation and genetics).^{47,48} Some patients labeled with Turcot syndrome have biallelic mismatch repair gene deletions, which

Fig. 1 Minute focus of signet ring cell adenocarcinoma in a 22-year-old woman with *CDH1* mutation. After undergoing surgery for a large, invasive gastric carcinoma, this patient opted for a total gastrectomy, which harbored nine additional submillimeter foci of malignancy, one of which is shown here.

has also been termed constitutional mismatch repair-deficiency syndrome.^{49,50} Many institutions have moved toward screening all cases of colorectal carcinoma for features of microsatellite instability, and this should be even more strongly considered in pediatric colorectal carcinoma not attributable to an already-known syndrome.

Finally, as with many other malignancies, colorectal carcinoma has been described in patients with Li-Fraumeni syndrome (germline *TP53* mutation), including those as young as 15.⁵¹ A more comprehensive review of this syndrome can be found elsewhere in this issue. Likewise, pediatric patients with Bloom syndrome have developed colon cancer (see section “Hematopoietic System”).

Not all syndrome-associated colorectal tumors are malignant adenocarcinomas. Patients with blue rubber bleb nevus

Fig. 2 Colonic Peutz-Jegher polyp harboring intramucosal carcinoma. The arborizing smooth muscle branches characteristic of this type of polyp can be visualized, along with the distinct transition from non-neoplastic to neoplastic, malignant epithelium.

syndrome develop multiple benign vascular venous malformations throughout their body, with the gastrointestinal tract being a characteristic site. It has been reported in children as young as 2 years.⁵² The syndrome appears to have an autosomal dominant pattern of inheritance and may be due to mutations in the *TEK* gene.⁵³

Neurofibromatosis type 1 (von Recklinghausen disease) is an autosomal dominant syndrome caused by *NF1* mutations and characterized by multiple neurofibromas throughout the body.⁵⁴ Numerous low-grade gastrointestinal tumors have been reported in these patients,⁵⁵ including multiple benign GISTs,⁵⁶ ampullary somatostatinomas (well-differentiated neuroendocrine tumors),⁵⁷ and intestinal ganglioneuromatosis.⁵⁸ However, these particular syndrome manifestations do not appear to occur in children,⁵⁹ and the most common pediatric gastrointestinal tumor in these patients remains visceral neurofibromas.⁶⁰ Germline *KIT* mutations, resulting in familial GIST syndrome,⁶¹ also rarely affect children, though one patient presented at the age of 18 years with a jejunal tumor.⁶²

Finally, intestinal ganglioneuromatosis is a known feature of multiple endocrine neoplasia syndrome 2B.⁶³ This family of syndromes is thoroughly discussed elsewhere in this issue. Nonsyndromic intestinal carcinomas in children may arise due to other predisposing conditions, such as inflammatory bowel disease.⁶⁴

Liver

Although liver tumors account for approximately 1% of cancers in children,^{65,66} there is a less extensive syndromic association compared to pediatric gastrointestinal tumors. The majority of childhood liver tumors are hepatoblastomas, and patients with Beckwith-Wiedemann syndrome have a markedly increased risk of developing one.⁶⁷ This syndrome, which can be sporadic or familial, is caused by a variety of defects in 11p15, including uniparental disomy.⁶⁸ Patients present with abdominal wall defects, macroglossia, macrosomia, hemihypertrophy, and hypoglycemia. They are also at an increased risk of developing a Wilms tumor (see section “Kidney”). Screening syndromic patients for hepatoblastoma (by abdominal ultrasound and serum α -fetoprotein levels) has been proposed and may improve outcomes.^{69,70} Several other syndromes also increase the risk of hepatoblastoma. These include familial adenomatous polyposis, Li-Fraumeni syndrome, and trisomy 18 (Edwards syndrome).⁶⁶

Hepatocellular carcinoma, while the second most common pediatric liver tumor, is far more common in adults than in children, as many causative factors (such as chronic viral hepatitis and steatohepatitis) take many years to cause sufficient liver damage. Its rate in children is naturally higher in regions with a higher prevalence of viral hepatitis. Certain syndromes do increase the risk of hepatocellular carcinoma in children,^{66,71} including hereditary tyrosinemia,⁷² type 1 glycogen storage disease,⁷³ Alagille syndrome,⁷⁴ Fanconi anemia,⁶ and possibly ataxia-telangiectasia.⁷⁵

Tuberous sclerosis (or tuberous sclerosis complex), which is discussed more thoroughly in the section “Kidney,” can rarely cause angiomyolipomas in the liver in children.⁶⁶

Pancreas

Pancreas tumors are very rare in children, and the few that arise are often not caused by a syndrome.⁷⁶ However, some genetic associations have been described. For example, pancreatoblastoma is the most common childhood pancreas tumor, and a few cases have been ascribed to Beckwith-Wiedemann syndrome.⁷⁷ Several syndromes also increase a pediatric patient's risk of developing pancreatic neuroendocrine tumors, including tuberous sclerosis (see section “Kidney”),⁷⁸ multiple endocrine neoplasia syndrome 1 (as discussed elsewhere in this issue), and von Hippel-Lindau disease (which can also cause serous cystadenomas, as also discussed elsewhere in this issue).

A few syndromes have been linked to increased risk of pancreatic adenocarcinomas in adults but not in children. These syndromes include Werner syndrome (an autosomal recessive disorder of *WRN* also known as “adult-onset progeria”),⁷⁹ dysplastic nevus syndrome (which results from *CDKN2A* mutation and also causes multiple melanocytic nevi),⁸⁰ and Peutz-Jeghers syndrome.^{36,37}

Kidney

In contrast to the organs described above, the kidney is a relatively common site for pediatric malignancies, harboring up to 7% of childhood tumors.⁸¹ By far the most common childhood tumor at this site is Wilms tumor (nephroblastoma).⁸² As with hepatoblastoma and hepatocellular carcinoma, several syndromes have been linked to development of Wilms tumor in children.^{82,83} These include WAGR syndrome (Wilms tumor, aniridia, genital anomalies, and mental retardation, resulting from deletion of 11p13), Denys-Drash syndrome (*WT1* mutation leading to a greater than 90% risk of tumor development), Frasier syndrome (*WT1* single nucleotide variants that may increase tumor risk), Beckwith-Wiedemann syndrome (see section “Liver”), *DICER1* mutations (which have also been linked to pediatric cystic nephroma⁸⁴; see section “Lung”), Li-Fraumeni syndrome, Fanconi anemia, trisomy 18, Bloom syndrome (see section “Hematopoietic System”), and Perlman syndrome, among others. Overall, up to 15% of Wilms tumors may be attributable to genetic predisposition.⁸²

Tuberous sclerosis is a fairly common syndrome that also can cause renal masses.^{81,85} It is caused by mutations in *TSC1* or *TSC2*, which are inherited in an autosomal dominant fashion in approximately one-third of cases and are sporadic in the remainder. This syndrome typically presents in infancy or childhood and first manifests as seizures and/or skin manifestations, such as Shagreen patches, facial angiofibromas, and ungual fibromas.⁸⁶ The classic kidney lesion in tuberous sclerosis is angiomyolipoma, a typically benign mesenchymal neoplasm composed of blood vessels, smooth muscle, and fat.^{81,85–87} Less commonly, these tumors can arise in the

liver.⁶⁶ Multiple renal cysts and, rarely, renal cell carcinoma can also occur in tuberous sclerosis patients.⁸⁸ Renal manifestations are a significant cause of morbidity and even mortality in tuberous sclerosis.⁸⁹ Other lesions also linked to this disease include cortical dysplasia (the “tubers” that give the syndrome its name), subependymal giant cell astrocytoma, retinal astrocytic hamartoma, cardiac rhabdomyoma (see section “Heart”), pulmonary lymphangiomyomatosis, various oral lesions, and the skin tumors mentioned above.⁸⁵ Renal angiomyolipomas have also been described in children with von Hippel-Lindau disease, Sturge-Weber syndrome (caused by *GNAQ* mutations), and neurofibromatosis.⁸¹

Renal cell carcinoma can also arise in children with genetic syndromes. In addition to angiomyolipoma, von Hippel-Lindau disease has been linked to pediatric renal cysts and renal cell carcinoma.^{81,90} Hereditary leiomyomatosis and renal cell carcinoma is a syndrome that stems from mutations in *FH*, which encodes fumarate hydratase. Various subtypes of renal cell carcinoma have been described in patients as young as 23 years old.⁹¹ Birt-Hogg-Dubé syndrome, resulting from *FLCN* mutations, causes skin fibrofolliculomas and a variety of renal cell carcinoma subtypes. These kidney tumors characteristically present around age 50 years but have been reported in patients in their third decade.^{92,93} An unusual subtype of renal cell carcinoma has recently been described in patients as young as 15 years who have germline mutations in succinate dehydrogenase genes.^{94,95} Patients with a *PTEN* mutation, such as those with Cowden syndrome, are also at an increased risk of developing renal cell carcinoma.^{32,38,96} Other suggested genetic abnormalities that may cause renal cancer include *BAP1* mutations, *MET* mutations (hereditary papillary renal cancer), and chromosome 3 translocations (familial clear cell renal cancer).⁹⁷

Finally, rhabdoid tumors of the kidney can arise in patients with rhabdoid tumor predisposition syndrome (see section “Brain”).

Prostate and Bladder

Prostate tumors are vanishingly rare in children. While family history is a strong risk factor for development of the disease, only a few genes have been tentatively implicated in this phenomenon, including *BRCA1*, *BRCA2*, and *HOXB13*.⁹⁸ Prostate cancer has rarely been reported in adults with Lynch syndrome.⁹⁹

Bladder tumors are also extremely rare in the pediatric population, with only approximately 100 cases reported in the literature.^{100,101} No particular syndromic associations have been established thus far, although variations in *NAT2* and *GSTM1* have been implicated in familial cases of bladder cancer.¹⁰² The risk of bladder cancer appears increased in some cases of Lynch syndrome, though this has not been reported in children.¹⁰³

Testis

In contrast to the prostate and bladder, the testis is a not an uncommon site of pediatric tumors, including rhabdomyosarcoma and germ cell tumors.¹⁰⁴ Despite this, relatively few

syndromic associations have emerged. The concept of familial testicular cancer has been reported but has not yet been linked to mutations in any particular genes.¹⁰⁵ Patients with Down syndrome (trisomy 21) appear to have a slightly increased risk of developing testicular germ cell tumors in childhood and young adulthood.¹⁰⁶ A few uncommon syndromes can lead to childhood testicular cancer, including testicular dysgenesis syndrome (also known as Frasier syndrome, which is caused by *WT1* abnormalities and can lead to development of gonadoblastoma and/or seminoma/dysgerminoma)^{82,107} and congenital adrenal hyperplasia (which can cause the rare and aptly named “testicular tumor of the adrenogenital syndrome” in nearly half of the cases).¹⁰⁸ Finally, *BRCA1* mutation appears to increase the risk of testicular tumor development.¹⁰⁹

Breast

Tumors of the breast are somewhat common in children, with masses occurring in approximately 3% of teenage girls. Nearly all of these are nonneoplastic processes or benign tumors, such as fibroadenomas and intraductal papillomas.^{110,111} Mammary carcinoma is very rare in children; its well-known association with mutations in *BRCA1* and *BRCA2* does not appear to increase risk in children carrying a mutation.¹¹² Similarly, while breast cancer is one of the most frequently occurring malignancies in patients with Li–Fraumeni syndrome, pediatric cases are distinctly uncommon.¹¹³ Additional genetic syndromes that increase the risk of breast cancer in adults, but not particularly in children, include ataxia-telangiectasia (a neurodegenerative disease caused by *ATM* mutations),¹¹⁴ Peutz–Jeghers syndrome (see section “Small and Large Intestine”), Cowden syndrome,^{38,115} and hereditary diffuse gastric cancer (germline *CDH1* mutation).¹¹⁶

Ovary, Cervix, Uterus, and Vagina

Tumors of the gynecologic tract are a prominent feature in a handful of cancer syndromes, though this rarely results in disease in the pediatric population. Lynch syndrome, although also known as “hereditary nonpolyposis colorectal cancer,” characteristically increases the risk of endometrial cancer in patients with germline mutations in mismatch repair genes.⁴⁴ However, the development of this cancer rarely occurs before the age of 30 years.^{117–119} Similarly, while *BRCA1* and *BRCA2* mutations cause hereditary breast and ovarian cancer, there are few if any reports of ovarian cancers arising in children with such mutations. In contrast, the noninheritable intersex condition Turner syndrome (female patient with only one active X chromosome) carries an increased risk of developing gonadoblastoma, especially in patients with some Y-chromosome material (such as 45,X/46,XY mosaics); this can occur at any age, including in infants.^{120,121}

A few other genetic syndromes can occasionally cause gynecologic malignancies in children. Reported examples include a 16-year-old girl with Peutz–Jeghers syndrome and a malignant ovarian Sertoli cell tumor,³⁷ a 15-year-old

girl with Cowden syndrome and endometrial cancer,¹²² uterine fibroids (leiomyomas) in an 18-year-old woman with hereditary leiomyomatosis and renal cell cancer syndrome,⁹⁰ and pediatric cases of ovarian Sertoli–Leydig cell tumor⁸⁴ and cervical embryonal rhabdomyosarcoma¹²³ caused by *DICER1* mutations, indicative of pleuropulmonary blastoma family tumor and dysplasia syndrome (see section “Lung”).

Heart

Cardiac tumors are rare in both the adult and pediatric population. When they do occur in children, they are often caused by a genetic syndrome.¹²⁴ For instance, up to 90% of cardiac rhabdomyomas are seen in patients with tuberous sclerosis (see section “Kidney”).^{125,126} These tumors are the most common pediatric heart tumor and sometimes can be diagnosed prenatally by fetal echocardiography.¹²⁶ Outcomes are extremely varied, as some rhabdomyomas spontaneously regress, while others cause severe cardiac symptoms leading to death.¹²⁵ Histologically, they are composed of benign, swollen myocytes with a polygonal shape and clear cytoplasm, giving rise to their pathognomonic “spider cell” appearance (► Fig. 3).

Another syndrome-associated tumor is the cardiac fibroma. About 3 to 5% of patients with this tumor have Gorlin syndrome (nevroid basal cell carcinoma syndrome), which is caused by inherited *PTCH1* mutations and leads to multiple basal cell carcinomas, odontogenic keratocysts, skeletal anomalies, and facial dysmorphism.¹²⁷ Fibromas are the second most common pediatric heart tumor and are composed of benign fibroblasts.¹²⁵ They can lead to cardiac dysfunction and even death.

Atrial myxomas are the most common heart tumor overall but are rare in children.¹²⁵ A small number of these tumors, including pediatric cases, occur in patients with Carney complex, which is caused primarily by *PRKAR1A* mutations

Fig. 3 Cardiac rhabdomyoma in a stillborn fetus. This large tumor, which caused cardiac failure and demise at 29 weeks' gestation, is composed of bland myocytes with swollen cytoplasm, giving them a so-called “spider cell” appearance.

and can present with a variety of manifestations, as evidenced by the formerly independent syndromes that have been incorporated into it (including LAMB [lentiginos, atrial myxomas, blue nevi] and NAME [nevi, atrial myxomas, myxoid neurofibromas, ephelides]).¹²⁸ These benign tumors have a bland myxoid appearance microscopically; like rhabdomyomas and fibromas, they are biologically benign but can lead to cardiac symptoms and patient demise. They often recur¹²⁵ and are responsible for ~50% of deaths in patients with Carney complex.¹²⁸

Lung

The lung is an unusual site for tumors in children, though a few genetic syndromes can cause them. One noteworthy example is pleuropulmonary blastoma family tumor and dysplasia syndrome, caused by *DICER1* mutations.⁸⁴ This syndrome can lead to a wide variety of pediatric tumors, including ovarian Sertoli-Leydig tumors, renal Wilms tumors, and cystic nephromas, thyroid cysts, and ciliary body medulloepitheliomas.^{84,129} The syndrome's eponymous lesion is a rare mesenchymal proliferation usually diagnosed before the age of 12 years.¹³⁰ It has been classified into three types based on whether the tumor is solid, cystic, or both, with solid components linked to metastasis and decreased survival.

As discussed above, tuberous sclerosis can lead to angiolipoma formation in the kidney and liver in children. A related proliferation of smooth muscle cells known as pulmonary lymphangioleiomyomatosis occurs in syndromic patients, including children on occasion.¹³¹ Carney triad (pulmonary chondroma, paraganglioma, and gastric GIST) often arises in children, with a median age of presentation of 21 years.¹³² Despite similar tumors appearing in children with familial succinate dehydrogenase gene mutations, no causative gene mutations in Carney triad have been confirmed to date, and the condition appears not to be heritable.¹³²

Brain

Several genetic syndromes that have been discussed above can result in the development of a brain tumor in a child. The hallmark of tuberous sclerosis is the "cortical tubers" (or cortical dysplasias) that form in the brain of 90% of affected patients.⁸⁵ Two additional major features of the disease are subependymal giant cell astrocytomas and subependymal nodules, which are unusual growths seen almost exclusively in tuberous sclerosis. Both are biologically benign but can cause neurologic symptoms due to mass effect.⁸⁵ Patients with a *PTEN* mutation causing Cowden syndrome can also develop a unique brain tumor: dysplastic cerebellar gangliocytoma. This hamartomatous proliferation is also known as Lhermitte-Duclos disease and typically arises in adult patients,¹³³ though some cases have been reported in young children,¹³⁴ including in an 8-year-old girl with neurofibromatosis type 1 rather than Cowden syndrome.¹³⁵ Children with Turcot syndrome

(a combination of intestinal polyposis and brain tumor) can develop medulloblastoma or the more lethal glioblastoma multiforme.^{47,48} Von Hippel-Lindau disease and multiple endocrine neoplasia type 1, which are both discussed elsewhere in this issue, can cause cerebellar hemangioblastomas and pituitary adenomas, respectively. Of note, medulloblastoma has also been described in children with Bloom syndrome (see section "Hematopoietic System").

Another syndrome responsible for pediatric brain cancer is the uncommon rhabdoid tumor predisposition syndrome, which results from constitutional *SMARCB1* or *SMARCA4* mutations.^{136,137} This syndrome causes a variety of tumors, including choroid plexus carcinomas, atypical teratoid/rhabdoid tumors, medulloblastomas, and schwannomatosis; as a result, patients can die at a young age. Loss of *SMARCB1* expression has been implicated in the pathogenesis of many tumor types in addition to the ones described so far in syndromic patients.¹³⁷

Eye

The most well-known pediatric eye tumor is probably retinoblastoma, which arises in retinal cells that have undergone biallelic inactivation of *RB1*.¹³⁸ The study of this exact phenomenon allowed Knudson to develop his "two-hit hypothesis" regarding mutational oncogenesis.¹³⁹ The tumor typically presents before age 3 and has a characteristic appearance on morphology, with small blue cells forming rosettes (→ Fig. 4). A variety of germline *RB1* mutations have been identified in retinoblastoma patients,¹⁴⁰ though the tumor is not always heritable. Rarely, patients with germline mutations can develop tumors in both eyes and in the suprasellar and/or pineal regions, causing "trilateral" or "tetralateral" disease.¹⁴¹

Other childhood eye tumors caused by inherited gene mutations include astrocytic hamartomas in patients with tuberous sclerosis,⁸⁵ retinal hemangioblastomas in von Hippel-Lindau disease, ciliary body medulloepitheliomas in

Fig. 4 Retinoblastoma in a 6-year-old girl. While retinoblastoma typically occurs in even younger patients, this tumor still demonstrates classic morphology, with small blue cells forming "rosette" structures.

patients with *DICER1* mutations,¹²⁹ bilateral optic pathway gliomas in neurofibromatosis type 1,¹⁴¹ and orbital rhabdomyosarcomas in several syndromes,¹⁴¹ including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, neurofibromatosis type 2, Noonan syndrome (a disease with numerous potential signs and symptoms that can be caused by *PTPN11*, *SOS1*, or *RAF1* mutations),^{142,143} and multiple endocrine neoplasia type 2A.

Thyroid

While thyroid cancer accounts for approximately 3% of tumors in children,¹⁴⁴ very few genetic syndromes can be blamed for their occurrence.¹⁴⁵ Medullary thyroid carcinoma in a child should prompt consideration of multiple endocrine neoplasia 2A (which also includes the outdated concept of “familial medullary thyroid carcinoma,” as discussed elsewhere in this issue). Cowden syndrome can lead to the development of follicular adenomas, follicular carcinomas, and papillary carcinomas of the thyroid.^{115,146} The rare cribriform-morular variant of papillary thyroid carcinomas is usually seen in children or young adults with familial adenomatous polyposis (as discussed elsewhere in this issue).^{147,148} Finally, thyroid carcinomas have been described in some patients with Wermer syndrome, as well as a few patients with Carney complex.¹⁴⁵

Adrenal

Neuroblastoma is the most common tumor of infancy.¹⁴⁹ This embryonal tumor can arise in the adrenal medulla, as well as the retroperitoneum and the paraspinal ganglia.¹⁵⁰ While the majority of cases are sporadic, hereditary examples have been linked to congenital central hypoventilation syndrome (caused by *PHOX2B* mutations), neurofibromatosis type 1, Noonan syndrome, and Beckwith-Wiedemann syndrome.^{67,142,143,149,150} Additionally, pheochromocytomas of the adrenal medulla can arise in multiple endocrine neoplasia, von Hippel-Lindau disease, neurofibromatosis, and hereditary paraganglioma-pheochromocytoma syndrome.^{23,150} Adrenal cortical carcinoma has been linked to Beckwith-Wiedemann syndrome and Li-Fraumeni syndrome.¹⁵⁰

Hematopoietic System

A wide variety of syndromes have been linked to the development of leukemia and lymphoma in childhood.¹⁵¹ Many of these fall under the category of chromosomal instability syndromes. One such example is Bloom syndrome, a rare autosomal recessive disorder caused by *BLM* mutations. Patients have a markedly increased risk of developing malignancy, including Hodgkin and non-Hodgkin lymphoma, acute leukemias, and epithelial tumors, such as colon cancer.¹⁵² These patients typically do not survive beyond their third decade.¹⁵³

Another chromosomal instability syndrome is Nijmegen breakage syndrome. This rare autosomal recessive disorder, characterized by *NBN* mutations, leads to skeletal anomalies,

other malformations, and a predisposition toward developing lymphoid malignancies, most commonly diffuse large B-cell lymphoma and T-cell lymphoblastic lymphoma.¹⁵⁴ Other types of hematopoietic malignancy have been described in this syndrome, as have sporadic reports of nonhematopoietic tumors.

Additional tendencies toward malignancy in chromosomal instability syndromes include acute myelogenous leukemia in Fanconi anemia (see section “Esophagus”) and various leukemias and lymphomas in ataxia-telangiectasia.^{114,155}

Autoimmune lymphoproliferative syndrome is an umbrella term for several conditions characterized by chronic lymphadenopathy and multilineage cytopenias.¹⁵⁶ Genes that can carry germline mutations in these disorders include *FAS*, *FASLG*, and *CASP10*, which all help regulate apoptosis. The median age at onset is 3 years, and patients carry an increased risk of developing B-cell lymphomas, often but not always after childhood.¹⁵⁷

Other syndromes that increase the risk of leukemia in childhood include Down syndrome¹⁵⁸ and Noonan syndrome.¹⁴³

Conclusion

Genetic syndromes can cause the development of pediatric tumors anywhere throughout the body, though certain organs are at higher risk than others. Development of either benign or malignant tumors in a child should suggest the possibility of an inherited syndrome, especially if the lesion is otherwise rare in the pediatric population. Recognition of such a syndrome can assist in optimal clinical management of not only the patient, but also the patient's family.

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