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Age-related biological differences in children's and adolescents' very rare tumors

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ABSTRACT

Very rare tumors (VRTs) in pediatric age represent many different diseases. They present an annual incidence < 2/1000,000 and correspond to about 11% of all cancers in patients aged 0–14 years. They can be roughly divided into two groups: one including tumors that are also rare in adults, and the other group includes adult-type tumors rarely encountered in children and adolescents. Although there is an obvious gap in knowledge regarding oncogenesis in pediatric cancers, there is some evidence of the involvement of various signalling pathways in the development of tumors in children and adolescents and sometimes in young adults. In addition, despite the rarity of these neoplasms, several attempts have been made to disclose the underlying mechanisms. More effort and resources have urgently to be devoted to deepening current knowledge and integrating new findings into the therapeutic approach, which nowadays relies on the treatment modalities used in adult oncology. The aim of this paper is to provide a review of the main solid VRTs occurring in both the pediatric and the adult age groups, highlighting the variability between groups in their biological and clinical course.

1. Introduction

Very Rare Tumors (VRTs) may be roughly divided into two groups: one includes tumors which are rare in both the pediatric and in the adult population; the other includes tumors, which frequently occur among adults, but are rarely observed in children, adolescents and young adults (adult-type VRT) [1]. However, the aetiology, biology and clinical course of some adult-type tumors seem to be different when they occur in children [2,3]. In spite of this, due to lack of evidence, diagnostic and treatment strategies for children affected by adult-type VRT are, in the

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majority of cases, adopted from those applied to adults, leading to either a worse prognosis or overtreatment in many cases [2].

In adults, most malignancies occur as a result of the accumulation of genetic somatic alterations following long-term exposure to carcinogens or spontaneously. In contrast, given the time required for the progressive accumulation of somatic genetic alterations, this oncogenetic hypothesis is not sufficient to explain the onset of cancer in children and adolescents [4].

In addition, several studies have underlined how cancer biology may change according to age, highlighting differences in genomic, transcriptomic, epigenetic, and immunological landscape, as well as in tumor histology and subtype distribution [5–9]. However, these reports mainly focus on adult oncology and generally do not include children and adolescents with cancer. Apart from predisposing germline pathogenic variants, which may explain only 10–20% of cancer in children and adolescents, some theories have been developed to better elucidate the mechanisms underlying the development of typical pediatric tumors [10].

Some authors support the hypothesis that most mutations occur during ontogenesis. A significant alteration in telomere length may occur before birth, leading to their accumulation before the end of puberty. This hypothesis would support that childhood cancer is a rare event, and that additional factors actually lead to the higher incidence with the increase of age [11].

Alternatively, a single catastrophic event leading to complex chromosomal rearrangements has been identified as a possible cause. However, since a similar event has never been proven, it has subsequently been postulated that tumor development may result from chromosome breakage (chromothripsis) during cell cycle progression [12–14]. The most intriguing hypothesis, which in part includes the previous ones, defines most pediatric cancers as a developmental disease, which occurs after a clonal genetic driver event. This may cause a maturation block, in specific cell lineages during defined developmental windows. In contrast, adult-type cancer is a result of an accumulation of mutations due to aging, cell division, and exposure to external mutagenic factors [15]. This theory may better explain the tight relationship of some pediatric tumors to developmental stages (i.e. neuroblastoma, acute lymphoblastic leukemia and a subgroup of adrenocortical tumors), their overlap with embryonal tissue (i.e. hepatoblastoma, Wilms tumor), and their spontaneous or chemo-induced differentiation (i.e. infant neuroblastoma and rhabdomyosarcoma respectively). Pediatric tumors generally show a lower burden of genetic aberrations and very limited immune cell infiltration and are therefore immunologically “cold” tumors [16].

Also, environmental risk factors have been considered to lead to the onset of cancer in children, but these studies fail to demonstrate a strong causative association, with the exception of the known role of chemotherapy and radiotherapy for second malignancies, and the role of infections as in Epstein-Barr virus-correlated neoplasms [4].

This review aims to delineate a summary of the current evidences available for some pediatric VRTs, either rare or occurring more commonly in adults, disclosing their clinical biological differences with the adult counterparts.

2. Adrenocortical tumors

Adrenocortical tumours (ACTs) account for approximately 0.2% of all childhood cancers, with an incidence around 0.2 new cases per 1 million children/year: the age incidence curve is characterized by two peaks, the first under 3 years and the second during adolescence [17–23]. ACTs comprise benign adenoma (ACA) and highly malignant carcinoma (ACC) and only recently, diagnostic and treatment recommendations were released at European level [24]. Overall, the presence of germline *TP53* pathogenic variants are a distinctive feature of pediatric ACT. Data on various levels (genetic, molecular, biological and epidemiological) confirm that pediatric ACT should be considered as a distinct disease from their adult counterpart.

Differentiating benign from malignant ACT is histologically difficult, and adult scores have been demonstrated to be poorly predictive in children [17,25–27]. It has been hypothesized that pediatric ACTs may arise from a cell resembling a phenotype of the foetal rather than the adult cortex. Thus, the benign course of ACA can be explained, despite the presence of impressively atypical microscopic features, as the consequence of a biological regression rather than a malignant phenotype [27].

The Wieneke index, first described in 2003, has been reported to have a prognostic value that is more reliable compared to other histologic prognostic scores used in adults [28]. Unfortunately, both the rarity of this disease and the high number of pathological features used make this index highly observer-dependant and does not allow for proper risk stratification (Table 1). More recently, Picard and al. described a 5-item microscopic score (Table 1) which allows to assess the risk of localised resectable tumors [29,30].

The *IGF2* (insulin-like growth factor 2) locus seems to play a critical role in determining the malignancy of both pediatric ACT and adult ACC due to the 11p15 LOH present in 91% and 82% of cases respectively; but with different proteins involved (IGF1R - insulin like growth factor 1 receptor in pediatric ACT and IGF2 in adults) [31,32].

Although aneuploidy caused both by chromosomal gains and deletions is common in both groups, amplification of chromosome 9q has been found only in pediatric cases: this region codes, among others, for NOTCH1R (Notch homolog 1 receptor, translocation-associated) and SF1 (steroidogenic factor 1), but SF1 over-expression has been found to predict a worse outcome only in adult ACC [33,34]. Chromosome 1p gain and 4q losses are seen more frequently in pediatric ACT [35].

Mutations in *CTNNB1* (catenin beta 1) and within the non-canonical Wnt/PCP (wingless/integrated - planar cell polarity) and Wnt/Ca2+ pathways are common in both groups and seem to be related to a worse outcome. On the other hand, additional mutations in the Wnt/β-catenin pathway (such as *ZNRF3*) were found only in adult tumours [36,37].

Chromatin remodelling pathways seem to be different, with pediatric tumors presenting *ATRX* (α-thalassemia mental retardation X-linked protein) mutations, while in adults also *MEN1* (multiple endocrine neoplasia 1), *DAXX (*Death-Associated Protein 6*), MED12* (Mediator of RNA polymerase II transcription, subunit 12 homolog) and *TERT* (telomerase reverse transcriptase) mutations can be detected [36]. Moreover, methylation profiles seem to differ significantly by age, too [38].

Another possible distinctive feature of pediatric ACT may be the expression of HLA (human leukocyte antigen) class II antigens, which were found downregulated in clinically malignant ACT [39,40]. Recently a single nucleotide polymorphism (SNP), rs9719074, in the alcohol dehydrogenase 7 gene involved in the retinoic acid pathway, was identified to be associated with a difference in the age-onset in both

Table 1
Details of the Wieneke Index and in the 5-item microscopic score.

Prognostic index	Pathologic criteria	Prognostic stratification
Wieneke Index	tumor size tumor weight extension into periadrenal soft tissues and/or adjacent organs vena cava invasion capsular invasion necrosis mitotic rate/atypical mitoses vascular invasion	Benign tumors ≤ 2 criteria Indetermined risk tumors 3 criteria Malignant tumors > 3 criteria
5-item microscopic score	adrenal capsular invasion venous invasion tumour necrosis mitoses > 15/20 high power fields Ki67 index > 15%	Favourable histology ≤ 2 criteria Unfavaourable histology > 2 criteria

group [34].

3. Colorectal cancers

Several reports have underlined that, though the incidence of colorectal carcinoma (CRC) in adolescents and young adults (AYA) is lower than in adults, it is indeed the fourth cause of death in AYAs affected by cancer [10]. AYAs with CRC present with higher rates of regional or metastatic disease at diagnosis (72% vs 50% in adults), with more aggressive histologic subtypes (mucinous subtype, signet ring, poorly differentiated tumors) (28% vs 17%), and show a poorer prognosis [10,41–44]. Another distinctive clinical feature is that distal tumors (transverse/left colon, rectum and sigmoid colon) seem to be more frequent in younger patients, up to 66% of cases [42,44,45]. Interestingly, it has been underlined that the poorer prognosis of CRC in AYA seems to be linked to disease-specific features rather than treatment disparities [42].

The rate of patients carrying a germline pathogenic variant ranges from 2% to 10% according to various authors [2,10,41,42], but Stoffel et al. reported that this rate may rise to around 20% of patients diagnosed with CRC before 50 years of age [46].

Common associated syndromes are Lynch syndrome or HNPCC (hereditary nonpolyposis colorectal carcinoma), and familial adenomatous polyposis (FAP). Pediatric and AYA CRC show high microsatellite instability (MSI) and a higher incidence of pathogenic variants in mismatch repair (MMR) genes, which are distinctive hallmarks of Lynch syndrome, but somatic methylation-induced silencing of the *MLH1* gene (MutL homolog 1) has also been observed in sporadic CRC in up to 20% of cases [44,47–51].

Genome-wide hypomethylation has been identified to characterize a subgroup of early-onset CRC with chromosome instability and to be a marker of poor prognosis [52]. In addition, more recent studies have shown, through WES (whole-exome sequencing) analysis, that AYA CRC show a distinct mutational profile, especially in genes involved in DNA repair pathways [53,54].

4. Breast cancer

Breast cancer in the pediatric population has a very low incidence, but with rising trends, and usually shows more aggressive features: larger tumor size, higher grade and often the absence of estrogen, progesterone and Her2 (human epidermal growth factor receptor 2) receptors (triple negative tumors) [10,55,56]. These characteristics lead to a worse prognosis than in adults.

In the elderly, clinical risk factors, such as previous ionizing radiation, use of contraceptive hormones, late age at first pregnancy, short or no breastfeeding, alcohol consumption, obesity, and physical inactivity, have been classically associated with the development of breast cancer. A low body mass index (BMI), may potentially increase the risk of breast cancer onset before the age of 18 years, and this, is the only reported risk factor for breast cancer in AYA [57].

The underlying biological differences have been the objects of a long debate and, so far, there are no clear and definitive evidences [10,58]. AYAs with breast cancer may carry a predisposing germline pathogenic variant, such as *TP53*, *BRCA1* (breast cancer gene 1) and *BRCA2* (breast cancer gene 2), in a significant rate [57,59], but this phenomenon does not fully explain the higher rate of aggressive and metastatic tumors seen in this age group.

Anders et al. found a differential expression of estrogen, progesterone, Her2 and EGFR (epidermal growth factor receptor) receptors and 367 gene sets overexpressed in the younger subgroup, but these findings failed to demonstrate to correlate with age, after correction for pathologic features [60–62].

A study by Johnson and colleagues disclosed that younger patients showed a relative overexpression of *BUB1* (budding uninhibited by benzimidazoles 1), *KRT5* (keratin 5), and *MYCN* (N-myc proto-oncogene protein), and underexpression of *CXCL2* (Chemokine - C-X-C motif - ligand 2), and these molecular abnormalities seem to correlate with age and outcome, after correction for tumor subtypes [63]. However, all these age-related differences in gene expression profiles, may explain the higher rate of clinically aggressive tumors in this age group rather than represent the tumor drivers [62].

5. Gastrointestinal stromal tumors (GIST)

The incidence of pediatric gastrointestinal stromal tumors (GISTs) is largely unknown due to their rarity in this age group. Nevertheless, they represent the most striking example of a unique biological and clinical behaviour in comparison with the adult counterparts [2,64].

Pediatric GISTs seem to affect mainly females and originate mostly from the stomach: at diagnosis, they tend to be metastatic in higher rates, and local and distant relapse are common. On the other hand, they appear to be indolent and more slow-growing in comparison to adult tumors, so that surgical resection is suggested only at presentation, when feasible, and if symptoms (bleeding, bowel obstruction) may impact patients' quality of life [65–67]. GISTs in the AYA group seem to share some mixed features and resemble both pediatric and late onset tumors [68].

Pediatric GISTs are predominantly wild-type for *KIT* (proto-oncogene c-KIT) and *PDGFRA* (platelet derived growth factor receptor alpha) genes (around 85%), and when children and adolescents with GIST present one of these pathogenic variants, they should be considered as having an adult-type GIST and treated accordingly [67]. Interestingly, although lacking the gain in the *KIT* gene, wild-type GISTs widely express a *KIT* activation that seems to highlight the role of this gene in GIST oncogenesis [2,69]. In addition, altered expression of genes of the insulin-like growth factor (IGF) signalling pathway may play an important role in GIST tumorigenesis and, with IGF1R (in pediatric cases) and IGF2 (in both groups) overexpression, may mediate primary or secondary resistance to imatinib [69].

Pathogenic variants of *SDH* (succinate dehydrogenase) *A*, *B* and *C* subunit (*SDHX* pathogenic variants) are the cause of Carney-Stratakis syndrome and are present in around half of wild-type GIST, while *SDHC* promoter specific-methylation are typical of wild-type GIST in the context of Carney triad; it needs to be emphasized that somatic *SDHX* mutations may not be associated to germline *SDHX* pathogenic variants (and to Carney-Stratakis syndrome). These findings led to the definition of two groups among pediatric GISTs: SDH-competent GIST and SDH-deficient GIST, with the latter lacking a gold standard systemic therapy. A more recent paper furtherly divided wild-type GIST according *SDH* status into three subgroups: SDH deficient with absence of SDHB expression, and/or presence of SDHX pathogenic variant and/or SDHC promoter specific methylation, with potentially relevant different clinical implications. The first group should be searched for kinase, *NF1* or *BRAF* pathogenic variants for a possible targeted therapy, the other two groups (altogether representing SDH-deficient GIST) may benefit of further research about the use of VEGFR inhibitors or DNA methyltransferase inhibitors [70].

6. Thyroid cancer

Differentiated thyroid carcinoma, represented mostly by papillary carcinomas (nearly 90%), is one of the most common endocrine tumors in children and adolescents [2,71,72]. The causative effect of radiation exposure has been demonstrated after the Chernobyl nuclear accident in 1986 and the increased frequency of thyroid cancer as second malignancy in patients irradiated for a primary tumor [73].

Pediatric cases of differentiated thyroid carcinoma are characterized by a high rate of multifocality, regional lymph node involvement, lymph vessel invasion, infiltration of surrounding tissue and distant metastases [74]. In addition, "microcarcinoma" (defined by a tumour $\leq$ 1 cm limited to the thyroid gland) is less common in the pediatric age, and is

frequently associated with multifocality, lymph node and distant metastases. In pediatric differentiated thyroid carcinoma, a high rate of relapse is seen [75]. Conversely, pediatric patients have an excellent outcome [76] with one exception – prepubertal / patients < 10 years [77]. Most strikingly but so far only incompletely understood, response to radioactive iodine treatment is inferior compared to adolescents and adults. An important hallmark of differentiated thyroid carcinoma in the pediatric age is represented by its response to TSH (thyroid-stimulating hormone)-suppression therapy, which is effective in controlling residual tumour growth. Hence, a more conservative approach in the pediatric age is still object of debate, although the current guidelines consider a total thyroidectomy followed by radioactive iodine therapy as the treatment of choice for these patients [78–80].

Pediatric thyroid carcinoma also presents biological differences in comparison with its adult counterparts [2,72]. Somatic fusion oncogenes have been found to be 3-fold more frequent in pediatric cases [81]: *RET* (Rearranged during transfection proto-oncogene) gene fusions are the most common findings (ranging from 25% to 30%) with *PTC1* (papillary thyroid carcinoma type 1) and *PTC3* (papillary thyroid carcinoma type 3) as the commonest partners. This rate may increase up to 45% in radiation-induced tumors [82].

Other reported somatic gene fusions involve *NTRK 1*, *2* and *3* (neurotrophic tyrosine receptor kinase genes), *BRAF* (proto-oncogene B-Raf) and *ALK* (anaplastic lymphoma kinase gene) [83] in a minor rate and usually presented by younger patients (< 10 years) [84], in particular *RET/NTRK* fusion seems to imply a major aggressiveness in comparison to tumors carrying *BRAF* and *RAS* (rat sarcoma virus gene) mutations [85].

BRAF p. V600E punctiform mutation, more common in adults, has been found more frequently in patients > 15 years of Hispanic ethnicity, and may identify a subgroup of tumors at higher risk and with a worse prognosis [81,83]. *TERT* mutations, which can be found in up to 20% of adult differentiated thyroid cancers and are considered distinctive of an aggressive disease, are uncommon in children [83].

A recent small series highlighted the role of somatic *DICER1* (helicase with RNase motif 1) mutations in follicular-patterned papillary thyroid carcinomas [86]. In addition, both somatic and germline DICER1 mutations were enriched in poorly differentiated follicular carcinomas in children and adolescents [87]. In pediatric patients with *DICER1* mutations, genetic counselling and testing should be advised for as a substantial number of patients are affected by DICER1 syndrome. Thyroblastoma, the most recently defined thyroid malignancy, represents an aggressive primitive blastic thyroid neoplasms with predilection for older children and young adults [88]. These tumors are defined by DICER1 mutations, all of reported cases to date had somatic (non-inherited) disease.

7. Malignant melanoma

In children under 15 years of age, the incidence of malignant melanoma (MM) is only 1.3–1.6 per million, but an exponential increase in incidence during adolescence leads to a rate that is already tenfold higher by age 15–19 [1]. This increase is probably related to greater cumulative sun exposure [89]. However, it is still unclear why in rare cases MM occurs at a young age, and its biological basis are not fully understood. The development of MM in adults involves a chain of mutational steps, and it usually does not develop soon after the first sunburns in childhood, but rather years or decades later. In addition, pediatric melanomas present differently than their adult counterparts, and there is evidence that they may be distinct entities [90]. While survival and prognostic factors in pediatric MM are generally comparable to adults [90], pediatric Spitzoid melanomas behave differently and need far less treatment. Studies have shown that classic pediatric MM have a similar genetic landscape to adult MM [91,92]. This involves driver mutations, mainly in *BRAF* and *PTEN*, kinase fusions, *CDKN2A* deletions, a high mutational burden, and UV alteration signatures. Data for Spitzoid melanoma are sparser, and it appears to be characterized more by fusions with *NTRK1*, *ROS1*, and *MET10* [92]. For the other subtypes (e.g., MM arising in congenital melanocytic nevi), data are only available from a few cases due to their rarity, suggesting a completely different pathogenesis including pathognomonic *NRAS* variants in the nevus component [91].

Interestingly, *MC1R* (melanocortin 1 receptor) gene variants have been found in up to 66% of MM patients. MC1R is a protein that plays a crucial role in determining human skin, hair, and eye colour. Variations in the *MC1R* gene can result in different variants of the protein, which can affect the production of melanin and result in variations in skin pigmentation. Additionally, *MC1R* variants appear to be more common in childhood and adolescent MM than in adult MM. Yet, the fact that we deal with low-risk genes suggests that other factors contribute to the development of pediatric melanoma that are currently unexplored. However, interestingly, analysis of inherited genetic variants rarely finds causative variants in known melanoma high-risk genes such as *CDKN2A*, *CDK4* or in DNA repair pathways in sporadic pediatric MM [93].

8. Lung carcinoma

The frequency of lung cancer subtypes in childhood differs markedly from the distribution in adults. Mucoepidermoid carcinoma (MEC) and adenocarcinoma (AC) are by far the most common subtypes, whereas squamous cell carcinoma, small cell lung carcinoma, and especially large cell carcinoma are particularly rare [94]. However, relevant biological differences have also been identified. Pediatric MEC of the lung are usually low-grade tumors characterized by typical *MECT1/MAML2* fusion transcripts, whereas high-grade MEC account for 20–30% of adult MEC [95,96]. Lymph node or distant metastases are less common than in adult MEC (10% vs. 17%), and survival is better than in adult MEC (95% vs. 72–89% 5-year OS) [96–98]. In pediatric AC of the lung, the frequency of metastatic spread is comparable to that of adults. However, genetic alterations seem to differ, even when compared to young adults. While *EGFR*, *BRAF*, *ERBB2*, *MET*, *ALK*, *RET*, and *ROS1* are among the most frequently altered genes causing adult lung AC in general (and *EGFR*, *ALK*, *ROS1* and *KRAS* in younger adults), *ALK* fusions and *KRAS* alterations seem to predominate in pediatric lung AC [97,99]. With a 5-year OS of 64% in pediatric patients with AC, survival is distinctly better than in adults (5-year OS 26%) despite 83% stage IV cancer [97]. Furthermore, RAS mutation in CPAM may be associated with mucinous adenocarcinomas and HPV-associated chronic laryngeal papillomatosis are more commonly associated with lung squamous carcinoma in childhood than in adults [97,100].

9. Conclusions

Most pediatric VRT, in comparison to their adult counterpart, seem to originate from different oncogenetic drivers and the clinical course may differ dramatically, being alternatively worse or better than that observed in adults. These differences attenuate with increasing age, with a progressive shift of tumor biology from the pediatric-type to the adult-type, as seen in the AYA group. As a consequence, the clinical approach for pediatric VRT should be driven by the specific molecular and clinical features present in this age group and adult-derived treatment strategies should be adapted and not merely transferred to pediatric patients.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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