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REVIEW

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Genotypes versus phenotypes: The potential paradigm shift in the diagnosis and management of pediatric neoplasms

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ABSTRACT

The gold standard of cancer diagnosis has long been based on histological characteristics. With the rapid advancement of genetic medicine, such standard algorithm of diagnostic approach is facing a challenge. The genetic findings have been changed from being a “supporting character” into the role of a “main character”. More and more disease diagnosis and classification has to be defined by genetic basis. In this article, we focus on the challenges in the field of pediatric oncology. We cited 2 scenarios where genetic information plays a pivotal role in identifying the underlying pathology. The first scenario is that same genetic mutation can lead to variable clinical phenotypes, this includes *EWSR1-PATZ1* fusion related neoplasms; *BCOR* neoplasms; and *GATA-2* deficiency related immunodeficiency and myelodysplastic syndrome. Another scenario is relatively more common that is the same clinical and histopathological phenotype with different underlying genotypes. The genotypes actually impact on the treatment response and outcome. We used medulloblastoma as an example. In fact, we can also find similar scenario in many pediatric cancers such as Ewing sarcoma, ependymoma, etc. The essence of this article is to remind clinicians of the rapid development in genetic medicine and it has been reshaping the landscape of the modern disease classification and therapeutic approach. In the near future, it may even lead to a paradigm shift in our disease diagnostic algorithm.

KEYWORDS

Genotype, Phenotype, Pediatric cancers

Introduction

In the early evolution of Western medicine, the diagnosis of diseases was mainly based on pattern recognition of clinical manifestations. Capturing accurate medical history and performing precise physical examination are indispensable skill that all clinicians have to acquire. Such traditional diagnostic maneuver remains a gold standard for a long while and is still very important for timely clinical management. Subsequently, the

industrial revolution led to rapid advances in technology. The gold standard in diagnosis gradually shifted to pathological methods. For cancers diagnosis, microscopic examination of the affected tissues obtained by biopsy is what we have been relying on since then. The use of immuno-histochemical staining further strengthened the reliability of such approach. Up to the current era, majority of pediatric cancers are classified based on specific histopathological findings. But in a significant number of cases, we may not be able to draw a definite

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conclusion by this approach. Under this circumstance, conflicting results may be given by different pathologists and the interpretation can be subjective. Another more common situation is that even with the same clinical and pathological classification of a specific cancer phenotype, we notice heterogeneity in the treatment outcome. What may contribute to this variation has been puzzling many oncologists for a long time. Effort in looking for risk factors based on either clinical features or biological markers has been applied over the past decades. Recently, with the rapid development in molecular genetics, we noticed that the heterogeneity of the same disease may be contributed by underlying genetic variances. Such genetic variations may affect the disease manifestations directly or indirectly, or it may affect the treatment response. We would like to highlight some of such situations and presented several cases as examples. We are foreseeing genetic and genomic information will inevitably impact on our future practice in pediatric oncology.

Same genetic mutation with variable clinical phenotypes

The conventional wisdom is that if we identify a specific genetic mutation, we expect the clinical phenotype will be similar across the board. In fact, the existing algorithm of pathological diagnosis is defined by the immunohistochemistry first and then verified by genetic information. In many occasions, the genetic information is considered as either academic interest or additional prognostic markers. But with molecular genetic testing getting more readily available and its usage becoming more widespread, we started to notice such algorithm may be misleading. In fact, clinicians notice under the same genetic aberration, very diverse clinical phenotypes and histological features can be derived. Several examples are cited here to illustrate such situation.

EWSR1-PATZ1 fusion related neoplasms

A 5-year-old boy was noted to have a swelling over his right angle of the mandible since he was 1.5-year-old. The swelling gradually increased in size and initial investigation by ultrasonography and CT scan showed a cystic mass with high vascular signal. He was treated empirically as vascular malformation with local sclerosing agent at a regional hospital. There was no response and the mass further progressed and some solid components started to emerge in repeated ultrasonography. The solid mass subsequently became the dominant part of the lesion. Biopsy was performed and it showed small blue round cell tumor and it was diagnosed as peripheral primitive neuroectodermal tumor (pPNET) with CD99 positivity. pPNET has a very diverse clinical pattern and is relatively more common in Chinese children.¹ He was eventually referred to us and the lesion already progressed into a large mandibular swelling with multiple lung metastases. Pathologists around the world

were consulted with different opinions given. The final consensus was “high grade undifferentiated tumor”. Specimens were sent for genetic testing using RNAseq panel including a variety of fusion genes and it turned out to be positive for *EWSR1-PATZ1*.² Then it was diagnosed as “*EWSR1-PATZ1* sarcoma”. He was treated according to the Ewing sarcoma regimen³ and he achieved good partial response with the treatment.

EWSR1-PATZ1 (Ewing Sarcoma Breakpoint Region 1 - POZ/BTB and AT Hook Containing Zinc Finger 1) gene fusion was first discovered in small round cell sarcoma.⁴ Later on, tumors with *EWSR1-PATZ1* fusion were found to exhibit highly variable clinical behavior which is distinct from Ewing sarcoma (Table 1). Their immunophenotype and pathological morphology also varies.⁵ Secondary genetic changes such as *CDKN2A/CDKN2B* loss are common and they contribute to oncogenesis. *EWSR1-PATZ1* neoplasm can present as a mass over the head and neck, chest wall, extremities or even lung. Interestingly, it can also present as brain tumors.⁶ There is no age and sex predilection and morphologically, it can be classified as undifferentiated sarcoma, alveolar rhabdomyosarcoma and primitive neuroectodermal tumor. In the brain, it can be diagnosed as glioma, primitive neuroectodermal tumor, and even pleomorphic xanthoastrocytoma.⁶ The immunophenotype does not show a consistent pattern.

TABLE 1 The *EWSR1-PATZ1* malignancies can be summarized as different categories

Type of tumor	Subtype
Sarcoma	Undifferentiated round cell sarcoma, alveolar rhabdomyosarcoma
Brain tumor	Primitive neuroectodermal tumor, pleomorphic xanthoastrocytoma, glioma, ganglioglioma, ventricular cystic glioneuronal tumor, undifferentiated sarcoma
Carcinoma	Soft tissue myoepithelial neoplasm

Then the problem arises, should we treat these tumors according to their histological classification or should we treat them based on the underlying genetic aberration? Due to the rarity of cases reported so far and they were mostly treated according to their respective histological classification, we do not have a clear answer to this question based on the current published data.

BCOR neoplasms

A 5-month-old girl was noted to have a cystic swelling over the dorsum of her left foot. Ultrasonography suggested lymphatic malformation. However, aspiration biopsy showed atypical spindle cells which were stained positive for CD99. It was diagnosed as pPNET by a renowned centre in China. It is known that pPNET can be found in infancy.⁷ But the family decided to seek 2nd opinion in another hospital, where incision biopsy was performed and the pathology suggested infantile

fibrosarcoma. However, genomic study failed to show any *NTRK* fusions. No treatment was offered while waiting for further study, the tumor progressed rapidly and she developed extensive lung, bone and lymph node metastasis within the next 4 months. She was brought to our hospital and after careful evaluation the diagnosis of primitive myxoid mesenchymal tumor of infancy was made.⁸ Immuno-histochemical stains showed that it was positive for both *BCOR* and *BC16*. Subsequent PCR confirmed *BCOR* internal tandem duplication (ITD) abnormality which is typical for *BCOR* sarcoma in infancy. She was treated with irinotecan and temozomide⁹ with the addition of apatinib¹⁰ and she achieved good partial response after 3 courses of treatment.

BCOR (*BCL-6* corepressor) is part of the noncanonical polycomb repressive complex 1 and its main function is to serve as an epigenetic control to regulate cellular differentiation in body structure development.¹¹ Germline *BCOR* loss-of-function mutations will lead to oculo-facio-cardio-dental syndrome, with an X-linked dominant inheritance. Somatic *BCOR* aberrations (mainly *BCOR-CCNB3*, *BCOR-MAML3* and *ZC3H7B-BCOR*), can drive the development of various sarcomas and CNS neoplasms (i.e. CNS HGNET-*BCOR*). Other loss of function mutations in *BCOR* recur in a large variety of mesenchymal, epithelial, neural and even hematological malignancies (Table 2).¹²

TABLE 2 The *BCOR* neoplasms can be summarized as different categories

Type of tumor	Subtype
Sarcoma	Clear cell sarcoma of kidneys, primitive myxoid mesenchymal tumor of infancy, undifferentiated sarcoma, EWS-like sarcoma (mostly with <i>CCNB3</i> fusion), round cell sarcoma of bone, rhabdomyosarcoma
Brain tumor	Medulloblastoma (esp. SHH subtype), high grade glioma, high grade embryonal tumor
Hemic malignancies	MDS, AML, CMML, NHL (rare forms such as EN-NK, T-NHL)
Carcinoma	Salivary glands CA, endometrial CA, thymic CA, etc

EWS, Ewing sarcoma; *CCNB3*, Cyclin B3; SHH, sonic hedgehog; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; NHL, non-Hodgkin lymphoma; EN-NK, extra nodal natural killer cells lymphoma; T-NHL, T non-Hodgkin lymphoma; CA, carcinoma.

***GATA-2* deficiency associated hematological malignancies & immunological disorders**

A 3-month-old girl presented with pallor and her complete blood picture showed pancytopenia. Bone marrow aspiration and trephine biopsy showed hypoplastic marrow and cytogenetic revealed monosomy 7. Deoxybutane (DEB) test did not demonstrate any increase in chromosomal breakage. Then repeated bone marrow examination 6 months later revealed hypoplasia with dysmegakaryopoiesis, compatible with myelodysplastic syndrome and karyotyping still showed

monosomy 7 abnormality. She was put on supportive care including occasional packed red blood cell transfusion while waiting for hematopoietic stem cell transplantation. Subsequently, molecular genetic test revealed that the patient has germline de novo heterozygous *GATA-2* mutation leading to haplo-insufficiency.

“GATA” is a family of transcription factors characterized by their ability to bind to the DNA sequence “-GATA-” and it consists of six proteins (*GATA-1* to 6). *GATA-1/2/3* are required for differentiation of mesoderm and ectoderm-derived tissues, including the hematopoietic and central nervous system,^{13,14} whereas *GATA-4/5/6* are implicated in the development and differentiation of endoderm- and mesoderm-derived tissues such as induction of differentiation of embryonic stem cells, cardiovascular embryogenesis and guidance of epithelial cell differentiation in the adult.

Three mutations are found in *GATA-2* deficient patients and they are truncating mutations prior to zinc finger 2 (*ZF2*); missense mutations within *ZF2*; and non-coding variants in the regulatory region of *GATA-2*.¹⁵ Germline *GATA-2* deficiency is associated with highly variable clinical phenotypes. It can be very mild such as in the case of sporadic neutropenia. However, some children present with a much more severe immunodeficiency due to the involvement of monocytic and lymphoid lineages (MonoMAC syndrome and DCML deficiency).^{16,17} Due to the underlying immunodeficiency, they may develop cutaneous atypical *Mycobacterium* infection¹⁸; recalcitrant periungual warts and perineal condyloma. In some patients, they may even have viral associated neoplasm such as Epstein-Barr Virus-related spindle cell tumor.¹⁹ Other from deficiency or dysfunction of the immune cells, they can develop myelodysplastic syndrome with monosomy 7 anomaly and some evolves into acute myeloid leukaemia.²⁰ In addition to the hematological anomalies, structural defect in terms of lymphatic malformation, congenital deafness, and pulmonary alveolar proteinosis can be found in some patients.²¹ The clinical spectrum of germline *GATA-2* deficiency is summarized in Table 3.

TABLE 3 The *GATA-2* deficiency clinical spectrum can be summarized into different categories

Syndromes	Features
Neutropenia	Unexplained neutropenia
MonoMAC syndrome	Monocytopenia with predisposition to non-tuberculous mycobacterial infection
DCML deficiency	Syndrome of low dendritic cells, monocytes, B and natural killer cells
Emberger syndrome	Primary lymphedema, congenital deafness, warts, low CD4
Familial MDS/AML	Early onset MDS/AML
Primary Childhood MDS	Childhood MDS

MonoMAC, monocytopenia and mycobacterial infection; DCML, dendritic cells, monocytes, B and natural killer lymphoid; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

The clinical hints to suspect GATA-2 deficiency including positive familial history and patients with myelodysplastic syndrome (MDS) associated with either monosomy 7 or trisomy 8.²² For adolescent with MDS associated with monosomy 7, up to 72% may have GATA-2 deficiency. And around 1/3 of childhood monosomy 7 syndrome are due to GATA-2 deficiency. Other manifestations of GATA-2 deficiency includes immunodeficiency (39%); B cells lymphopenia; lymphedema with or without hydrocele (23%); congenital deafness (9%); urinary tract anomalies including vesicoureteric reflux and kidney asymmetry (12%); and behavioral problems such as attention deficit and hyperactive disorders or autism (12%).

Same clinical and pathological phenotypes with different genotypes

Since the same genetic aberration may lead to highly variable disease phenotypes, we should naturally expect under the same histologically defined disease, there may be different genetic mutations. We noticed these genetic mutations also implicate on the clinical outcome. This makes molecular genetic testing an essential component of modern diagnostic armamentarium. There are several examples to support this observation.

Medulloblastoma with variable genetic mutations

A 14-month-old infant presented with history of on and off vomiting and irritability for the past 4 weeks. The vomiting was just once in a few days initially but lately, the frequency increased to almost daily and his parents noted that he developed convergent squint and refused walking. MRI showed a huge cerebellar tumor arising from the vermis and obliterating the 4th ventricle with obstructive hydrocephalus. Emergent external shunt was performed and then the tumor was gross totally removed. Histology was compatible with medulloblastoma of classical morphology and molecular genetic profile matched that of Group 3 subgroup with *C-MYC* amplification. Subsequent spine MRI showed multiple small nodular metastases over the leptomeningeal canal. He was given chemotherapy based on the HeadStart

regimen²³ with the intention to avoid irradiation. After 5 courses of chemotherapy, he achieved stable disease status but the spinal lesions persisted.

For medulloblastoma, it was traditionally classified into classical, desmoplastic [nodular & extensive nodular, (DN & EN)] and large cell anaplastic (LCA) types based on morphological characteristics.²⁴ The prognosis differs among these morphological types but some heterogeneity was noted. We can now reclassify them more precisely into 4 major subgroups based on underlying somatic molecular genetic aberrations.^{25,26} The current data shows that the same morphological classification may have different genetic aberrations which impact on the prognosis. The clinical phenotype and prognosis correlate better with the molecular genetic subtype rather than the histological phenotype (Table 4).²⁷ Lately, further molecular subgrouping can define the prognosis even better.²⁸

In the past, infant with medulloblastoma is considered as having poor prognosis with the exception of those with desmoplastic histology. It was speculated that it is due to the avoidance or delay of irradiation accounting for such adverse outcome. With the genetic grouping available, we can have a clearer insight of the underlying reason and this also helps us to design appropriate treatment strategy in the future.

Discussion

With the advancement of molecular genetic technology, genetic information is becoming more readily available and affordable. More and more new data can now be gathered to re-classify pediatric neoplastic disorders. It gives us insight as of how the genetic mutation may impact on the disease development, biological characteristics, disease phenotype, treatment response and prognosis. In this article, we cited several examples to illustrate the fact that: 1) same genetic mutation can lead to variable clinical phenotypes; 2) same clinical and pathological phenotype can have different underlying genetic aberrations. Actually, these 2 observations are like mirror images verifying the

TABLE 4 Medulloblastoma can be summarized as 4 molecular genetic subgroups and they have overlapping morphological diagnosis

Group	Clinical phenotype	Morphology & prognosis	Signature genetic aberration and gene expression	Chromosomal abnormalities
WNT	More in adolescent, M = F, rarely metastasis	Classic, very good	<i>CTNNB1</i> mutation (<i>C-MYC</i> amplification +)	6-
Sonic Hedgehog (SHH)	More in either infant or older children, M=F, uncommonly metastasis	Desmoplastic, classic and LCA, infants good, other intermediate	<i>PTCH1/SMO/SUFU</i> mutation (<i>GLI2</i> amplification, <i>MYCN</i> amplification +)	3q+, 9q-, 10q-
Group 3	More in infant & young children, M>F, frequently metastasis	Classic and LCA, very poor	Nrl (Photoreceptor/GABAergic) (<i>C-MYC</i> amplification +++)	1q+, 7+, 17q+, i17q, 18q+, 5q-, 8-, 10q-, 11p-, 16q-
Group 4	More in young children, M>F, frequently metastasis	Classic and LCA, intermediate	Nrl (Neuronal / Glutamatergic) (<i>CDK6</i> amplification, Seldom with either <i>MYC</i> amplification)	7+, 17q+, 18q+, x-, 8-, 11p-

M, male; F, female; LCA, large cell anaplastic.

same philosophy that the genetic diagnosis is important in disease classification. We need to rely on such information to stratify our patients more precisely and accurately for designated treatment.

The classical approach of pathological diagnosis for childhood cancers is to get the tissue and performed immuno-histochemical stains, the diagnosis is based on both morphology under the microscope and the expression of specific disease related proteins. But in recent years, we noticed that we have to rely more and more on the genetic information in order to stratify the patients into different risk groups. This risk stratified treatment approach is the standard for childhood acute lymphoblastic leukemia nowadays. In addition, the genetic mutation information can help us to perform minimal residual disease monitoring so timely treatment modification can be instituted. Furthermore, some genetic mutations can identify actionable targets so specific targeted therapy can be applied.^{29,30}

Pediatric sarcomas and brain tumors are known to have highly variable histological classification based on traditional immunohistochemical approach. Their development in management has been lagging behind that of pediatric leukemia, partly it is due to the relative difficulty in getting tissue for diagnosis when compares to leukemia, and also the rarity of each specific type of tumors. With the help of molecular diagnostic technology, many hindrances in the past have been overcome. The molecular diagnosis usually needs a relatively small amount of tissue. With the success of liquid phase biopsy, the progress of certain solid tumors such as metastatic neuroblastoma and rhabdomyosarcoma can now be monitored by either bone marrow or even peripheral blood samples.^{31,32}

But when we propose to apply genetic diagnosis, it is not just confining to a few commonly used techniques such as RT-PCR, FISH, panel NGS³³ or sequencing (WES or WGS).³⁴ In recent years, the molecular genetic diagnostic approach also extends to looking at the transcriptome (i.e. RNAseq)³⁵ and epigenetic profiles including the methylation profile; histone acetylation profile; expression of miRNA; and other non-coding RNAs. For example, undifferentiated sarcoma³⁶ and pediatric central nervous system primitive neuroectodermal tumor³⁷ have been reclassified by the methylation profile and it reveals interesting yet complex pattern of different diseases being classified into a single category previously.

Even for the molecular diagnosis approach, there are disagreements on the approach. In adult solid tumors, most laboratories tend to perform panel NGS as the initial screening. If it fails, then most pathologists will proceed to either WES or WGS. Such algorithm may not be suitable for pediatric solid tumors due to the rarity and highly complex categories involved. Therefore, some pathologists

prefer to go for WES or even WGS right away when they encounter difficult cases. It will depend on the strength of bioinformatics support if such approach is adopted for vast amount of data can be generated and it may be confusing to interpret.

Another argument is whether we should adopt a histological approach first followed by genetic confirmation or genetic approach first followed by histological confirmation? It is a difficult and complex question to answer. Most pathologists will prefer the histological approach and supplement with genetic testing. However, we start to notice an emerging reversed, that means some pathology laboratory just performed minimal histological tests for screening and then jumped to the genetic testing right away. Despite criticism, whether this approach will become the main approach remains to be observed. Some even foresees that such scenario is comparable to the story of digital camera versus filmed camera, the outcome eventually will be decided by the consumers. In this regards, the patients and the clinicians are the consumers and their preference may influence the outcome of such development.

No matter which algorithm that we follow, the best approach nowadays is to have a multi-disciplinary tumor board so the clinical information, imaging characteristics, pathological findings and genetic data can all be integrated before logical therapeutic approach can be formulated. For pediatric tumors, due to the rarity of specific tumor types, international collaboration is highly recommended so the genomic and epigenomic data can be shared and properly analyzed.

To summarize, pediatric cancers are rare and yet with many varieties based on histological classifications. The rarity and heterogeneity issues among different tumor types often create difficulties for the clinicians in conducting clinical studies. It is because it often takes years to recruit adequate subjects to answer the questions. With the rapid development of genetic and genomic medicine, more precise grouping and classification can now be achieved and this also means the required study sample size will be even more difficult to fulfill. There should be an international effort to coordinate clinical study based on the new diagnostic information. In the past, most clinical trials for pediatric cancers were conducted in America and Europe. With 70% of world population residing in Asia and the basic health care condition improving, new paradigm has to be established. The Asian pediatric pathologists and oncologists should work together to set up a common platform for clinical trial. Then we can work with our colleagues around the world to advance our knowledge in managing childhood cancers.

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CONFLICT OF INTEREST

None.

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