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CORRESPONDENCE

DICER1-associated sarcomas: towards a unified nomenclature

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To the Editor:

We read with interest the recent paper by Schultz et al. "Pleuropulmonary Blastoma-like Peritoneal Sarcoma: a Newly Described Malignancy Associated with Biallelic *DICER1* Pathogenic Variation" [1]. The spectrum of reported *DICER1*-associated sarcomas continues to expand, and in this paper the authors report 7 cases of a primitive sarcoma that resembles pleuropulmonary blastoma (PPB). The tumours exhibited *DICER1* pathogenic variants (hereafter referred to as "mutations"), were located in the peritoneal cavity and occurred in children at a mean of age 13 years (range 3–14 years). It appears that two of these neoplasms (cases 1 and 4) represent the same tumours we recently reported as embryonal rhabdomyosarcomas of the fallopian tube associated with *DICER1* mutations [2]; our paper would not have been published when the authors were putting together their series of cases. Both these tumours, in common with some of the other neoplasms reported by Schultz et al. (the exact number is difficult to determine from the limited pathological details), exhibited rhabdomyoblastic differentiation (myogenin and myoD1 positivity) and contained cartilaginous elements.

Our purpose of writing this letter is to point out that *DICER1*-associated sarcomas in many anatomical locations, and not just the peritoneum, exhibit a very similar and characteristic histology and closely resemble PPB from a morphological point of view; the sites where these neoplasms have been reported continues to increase and is likely to expand in the future. We concur with the views of Warren et al., who, also publishing in *Modern Pathology*, presented three new cases of DICER1-associated sarcoma and undertook a comprehensive review of the literature of 83 other cases, and suggested that these neoplasms, regardless of their site of origin, exhibit characteristic morphological features that resemble PPB [3]. These include a subepithelial layer of malignant mesenchymal cells, areas of rhabdomyoblastic differentiation (embryonal rhabdomyosarcoma) with positive staining with myogenin and myoD1, cellular/ immature and sometimes overtly malignant cartilage, foci of bone/ osteoid and foci of anaplasia. Not all of these characteristic features are present in every case.

Such neoplasms have a different terminology at different sites, for example PPB, PPB-like peritoneal sarcoma [1], *DICER1*-associated central nervous system sarcoma, spindle cell sarcoma with rhabdomyosarcoma-like features, *DICER1* mutant, primary intracranial sarcoma, *DICER1*-mutant [4–6], *DICER1* renal sarcoma, anaplastic sarcoma of the kidney [7, 8] and presacral malignant teratoid neoplasm in association with pathogenic *DICER1* variation [9], to name a few.

A further interesting and related point is that embryonal rhabdomyosarcomas of the uterine cervix, endometrium and ovary are established to be associated with *DICER1* mutations [10, 11] and these also often exhibit the characteristic morphological appearance described with subepithelial condensation of tumour cells, cartilaginous differentiation and areas of anaplasia. Intracranial embryonal rhabdomyosarcomas have also been reported to exhibit *DICER1* mutations [12] and, as noted by the authors [12], it is likely that these represent the same tumour type as those reported as primary intracranial sarcoma, *DICER1*-mutant or as DICER1-associated central nervous system sarcoma [4, 5].

In an ideal situation, it would be desirable if a unified nomenclature could be used to reflect that these neoplasms in different organs are likely to be part of the same tumour spectrum and strongly associated with *DICER1* mutations, whether germline (as part of DICER1 syndrome) or somatic (post-zygotic, and generally not syndromic). For example, unifying terms such as "primary intracranial sarcoma,

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DICER1-mutant", "primary peritoneal sarcoma, *DICER1*-mutant" or primary cervical sarcoma, *DICER1*-mutant" could be used. However, we appreciate that in the real world, nomenclature changes have the potential to result in confusion for pathologists and clinicians given that it may not be apparent that these "new" terms refer to neoplasms, which are already referred to by established terms in the literature rather than newly defined tumour types. This could potentially result in "loss" of important information when new terms are used since the pertinent literature may not be reviewed. However, we think it would be desirable to somehow unify the nomenclature and this will require close cooperation between pathologists and clinicians dealing with these rare tumour types; this will be required to be followed by adoption by groups which are responsible for tumour classification, such as the International Agency for Research on Cancer (IARC), the organisation that is responsible for producing the World Health Organization (WHO) "Blue books" on tumour classification. When introducing such a new terminology, it may be prudent to initially use both the "new" and "old" names, for example "primary peritoneal sarcoma, *DICER1*-mutant (PPB-like peritoneal sarcoma)", "primary pulmonary sarcoma, *DICER1*-mutant (PPB)" or "primary cervical sarcoma, *DICER1*-mutant (cervical embryonal rhabdomyosarcoma)".

A broader point to be appreciated by pathologists (and clinicians) is that, especially but not exclusively in a young patient, when dealing with a mesenchymal neoplasm with areas of skeletal muscle differentiation/ embryonal rhabdomyosarcoma, cellular cartilage and/or anaplasia, the potential involvement of *DICER1* should be considered and appropriate tumour testing undertaken. This is important since some of these patients will have germline *DICER1* mutations (DICER1 syndrome) and, if this is established, surveillance/ screening can be undertaken for other *DICER1*-associated neoplasms and family members can be tested. Any person whose tumour contains a *DICER1* mutation should be considered to be at risk for DICER1 syndrome, until proven otherwise [3].

As molecular diagnostics increase in availability and sophistication, similar or identical molecular events are being identified in tumours arising at diverse sites which often go by different names but have similar morphology. A good example of this is *SMARCA4* mutations in small cell carcinoma of the ovary of hypercalcaemic type (SCCOHT) [13–17], as well as in a variety of other neoplasms, for example within the uterine corpus, lung, gastrointestinal tract, pancreas, head and neck and other sites. These are often characterised by a monotonous population of cells, sometimes with rhabdoid features, and a similar morphological appearance to SCCOHT [18–26]; in different organs, these neoplasms have variably been designated as carcinomas or sarcomas. While it would be more correct to refer to these by a generic term such as *SMARCA4* deficient malignancies, we also recognise that, like PPB, some of the terms, for example SCCOHT, are well established in the literature and are likely to remain; as such, using both the "new" and "old" terminologies may be advisable in the immediate future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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