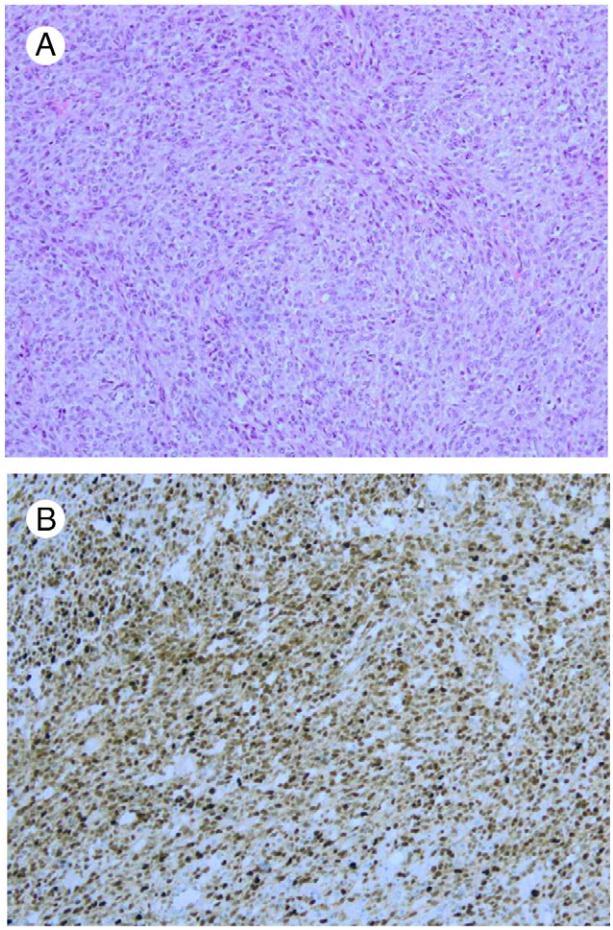

Fig. 2 A, Histology of a *CIC-DUX4* fusion–positive round cell sarcoma (hematoxylin and eosin, ×100). B, Strong and diffuse cyclin D1 expression in *CIC-DUX4* fusion–positive round cell sarcoma (×100).

expression was observed in all 4 cases (Fig. 2). Therefore, cyclin D1 expression is not helpful in differentiating this subgroup of fusion-positive round cell sarcomas from classical EWS.

So, diffuse and strong cyclin D1 expression can be used as a sensitive, although not specific, biomarker for EWS and neuroblastoma, keeping in mind that cyclin D1 expression can be seen in other, more rare small blue round cell tumors, like CCSK and *CIC-DUX4* fusion–positive round cell sarcomas.

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Diagnostic utility of cyclin D1 in the diagnosis of small round blue cell tumors in children and adolescents: beware of cyclin D1 expression in clear cell sarcoma of the kidney and *CIC-DUX4* fusion–positive sarcomas. Comment on Magro et al (2016)—reply

Dear Editor:

We would like to thank Creytens et al for their fruitful comments about our article on the diagnostic utility of cyclin D1 in the differential diagnosis of small round blue cell tumors in children and adolescents [1]. They showed that a diffuse expression of cyclin D1 can be also found in round cell sarcomas harboring *CIC-DUX4* gene fusion, similarly to Ewing sarcoma (EWS). Accordingly, they stated that cyclin D1 is not helpful in differentiating these 2 entities. The present letter gives us the opportunity to present our preliminary results about cyclin D1 expression in a series of undifferentiated sarcomas of infancy.

As reported in the discussion of our article [1], we are aware that a new group of small round cell sarcomas of childhood and young adults, with morphological and immunohistochemical overlap with EWS, has been emerging over the last years [2]. A significant number of these neoplasms, labeled with the generic term *Ewing-like sarcomas*, exhibit an atypical histology and often unusual location (intra-abdominal or superficial masses) and lack specific translocations when compared with EWS [3]. Although molecular tests fail to detect any gene fusion transcripts in a subset of these neoplasms (undifferentiated small round cell sarcomas, not otherwise specified), an

increasing number of distinctive genetic alterations are being achieved, especially the *CIC-DUX4* or *BCOR-CCNB3* gene fusions [2]. Recently, Kao et al [3] contributed to expand the spectrum of *Ewing-like sarcomas*, emphasizing that a subset of undifferentiated round cell sarcoma and the so-called "primitive mesenchymal myxoid tumor of infancy" (PMMTI) could represent the soft tissue counterpart to clear cell sarcoma of the kidney (CSSK). The link among these 3 tumors was based on the evidence that they share, at least partially, morphologic, immunohistochemical, as well as genetic alterations, especially *BCOR* exon 16 internal tandem duplications (*BCOR* ITD) [3].

As it is well known that CSSK overexpresses cyclin D1 [4], we tested immunohistochemically this immunomarker in some cases of soft tissue undifferentiated round cell sarcoma of infancy with recurrent *BCOR* ITD included in the previously mentioned article by Kao et al [3]. In this regard, we selected 13 cases of *BCOR* ITD–positive sarcomas, including 7 cases of undifferentiated round cell/Ewing-like sarcomas and 6 cases of PMMTI, occurring in infants (age ranging from 23 days to 11 months; Table). Interestingly, in all but one case was a strong and diffuse (>70% of neoplastic cells) cyclin D1 immunoreactivity obtained (Figure). This finding, revealing that cyclin D1 is overexpressed in *BCOR* ITD–positive sarcomas, is additional evidence that CSSK, Ewing-like undifferentiated round cell sarcoma, and PMMTI are likely in the spectrum of a single morphobiological entity. Apart from EWS, our results and those obtained by Creytens et al suggest that cyclin D1 is helpful in identifying Ewing-like sarcomas with *EWS/CIC-DUX4* fusion or *BCOR* ITD, prompting pathologists to perform genetic and/or molecular studies as confirmatory tests.

Finally, Creytens et al in their Letter to the Editor underlined that cyclin D1 does not distinguish CSSK with round cell morphology from EWS primarily arising in the kidney. As previously stated in our article, we state again that cyclin D1 should never be used as a sole marker for diagnosis but always as part of a panel of immunostains and should be evaluated in the appropriate clinicopathologic context [1].

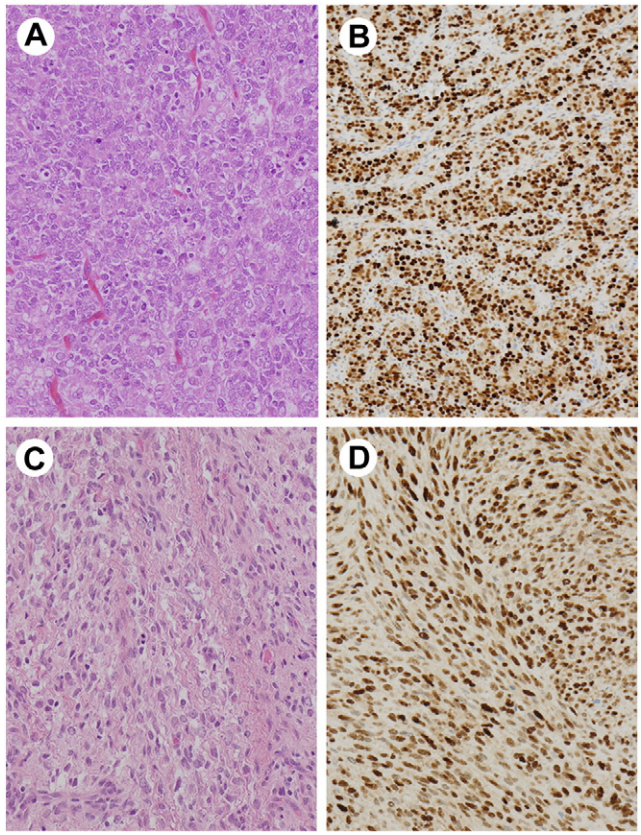

Figure A and B, Undifferentiated round cell sarcoma/atypical EWS is diffusely stained with cyclin D1. C and D, PMMTI showing diffuse expression of cyclin D1.

Table Clinicopathologic findings of *BCOR* ITD sarcomas and cyclin D1 expression

Case	Age/sex	Morphological diagnosis	Site	*BCOR* ITD	Cyclin D1
1	10 mo/M	URCS	Paravertebral	Positive	Negative
2	3 mo/M	URCS	Retroperitoneum	Positive	Positive
3	23 d/M	URCS	Back	Positive	Positive
4	11 mo/M	Atypical EWS	Chest wall	Positive	Positive
5	5 mo/M	Atypical EWS	Retroperitoneum/pelvis	Positive	Positive
6	3 mo/F	Atypical EWS	Jaw	Positive	Positive
7	8 d/F	Atypical EWS	Buttock	Positive	Positive
8	6 mo/M	PMMTI	Retroperitoneum	Positive	Positive
9	10 mo/F	PMMTI	Abdominal cavity	Positive	Positive
10	4 mo/F	PMMTI	Paravertebral region	Positive	Positive
11	2 mo/M	PMMTI	Paraspinal region	Positive	Positive
12	9 mo/F	PMMTI	Abdominal wall	Positive	Positive
13	5 mo/M	PMMTI	Larynx	Positive	Positive

Abbreviation: URCS, undifferentiated round cell sarcoma.

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