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Presacral malignant teratoid neoplasm in association with pathogenic *DICER1* variation

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Abstract

We report two malignant sacrococcygeal tumors in infants that were associated with pathogenic *DICER1* variation. These tumors were composed of primitive neuroepithelium, embryonal

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Conflict of Interest

The authors declare no conflicts of interest associated with this manuscript.

rhabdomyosarcoma and cartilage and initially diagnosed as immature teratomas. One child developed intracranial metastasis and died. The second child underwent surgery and chemotherapy and achieved complete remission. This child subsequently developed five additional *DICER1*-associated neoplasms by age nine. Genetic analysis revealed that both tumors harbored biallelic pathogenic *DICER1* variation. We believe these cases represent another novel subtype of *DICER1*-associated tumor. This new entity, which we propose to call *DICER1*-associated presacral malignant teratoid neoplasm, may be difficult initially to distinguish from immature teratoma, but recognizing it as an entity can facilitate appropriate classification as an aggressive malignancy and facilitate appropriate genetic counseling, *DICER1* germline variant testing, screening and education.

Keywords

Immature teratoma; sacrococcygeal teratoma; yolk sac tumor; neural plate; *DICER1*; *DICER1* syndrome; intracranial metastasis

Introduction

DICER1 encodes an RNase III endonuclease and plays a pivotal role in miRNA processing [1]. Since it was first reported as the causative gene for familial pleuropulmonary blastoma, pathogenic *DICER1* germline variation has been identified in a number of tumor types of seemingly diverse histogenesis including pleuropulmonary blastoma, ovarian Sertoli-Leydig cell tumor, cystic nephroma and pituitary blastoma and some non-cancerous conditions, including multinodular goiter and macrocephaly [2–6]. *DICER1*-associated tumors typically harbor biallelic *DICER1* variation: a loss-of-function variant (usually germline) and a somatic “hotspot” variant within the RNase IIIb domain (E1705, D1709, G1809, D1810, or E1813). Here, we report two infants who had pathologically unique presacral tumors that harbored biallelic *DICER1* variants. We would propose that these neoplasms with their collage of dysembryonic tissue patterns, initially interpreted as immature teratomas, represent another unique *DICER1*-related tumor. However, the various pathologic representatives in these neoplasms overlapped to a considerable degree with the other *DICER1*-related dysontogenetic neoplasms with their own teratoid morphologic attributes.

Material and Methods

Human subjects review.

The study was approved by the Institutional Review Boards at all participating institutions. Patient 1 was enrolled in the Japanese Children’s Cancer Group observational study. Patient 2 was enrolled in the National Cancer Institute Natural History of *DICER1* Syndrome study (NCT-01257597). Eligibility criteria included a history of a *DICER1*-associated neoplasm or documentation of a pathogenic germline *DICER1* variant. Informed, written consent was obtained from the patients’ parents.

DICER1 genetic analyses.

For the tumor from patient 1, targeted sequencing for all coding exons from 93 genes (Supplemental Table 1) was performed on an Ion Proton Sequencer (Life Technologies). Reads were mapped onto the hg19 human reference genome sequence and common variation from dbSNP build (<http://www.ncbi.nlm.nih.gov/projects/SNP/>), the 1000 Genomes database (<http://www.1000genomes.org>), and Human Genetic Variation Database (<http://www.hgvd.genome.med.kyoto-u.ac.jp/>) was excluded. In Patient 2, germline *DICER1* testing was performed by Invitae on DNA extracted from blood. Somatic *DICER1* sequencing of the tumor performed on DNA extracted from the paraffin block was performed as previously described [7].

Results

Patient 1

A one-week-old boy was admitted because of loss of lower extremity movement. His prenatal period and family history were unremarkable. Magnetic resonance imaging showed an extradural tumor within the spinal canal extending from L2 to the sacral region (Fig. 1A, B). The levels of serum alpha-fetoprotein and β -human chorionic gonadotropin were within the normal ranges for his age. Following the partial resection of a hemorrhagic mass, the patient received one course of chemotherapy with etoposide and carboplatin and subsequently underwent gross total resection. Pathologic examination of the resected masses revealed a multi-patterned neoplasm composed of primitive neuroepithelial and mesenchymal elements. The neuroepithelial components consisted of primitive neuronal cells forming occasional true rosettes with a resemblance to medulloepithelioma (Fig. 2A, B). There were scattered nodules of primitive cartilage rimmed by spindle cells (Fig. 2C). The remainder of the tumor was composed of embryonal rhabdomyosarcoma showing a full range of differentiation from blastema to maturing skeletal muscle (Fig. 2D). Neither epithelial lined cysts, cutaneous structures, or fetal-appearing tissues like liver or pancreas nor malignant germ cell elements like endodermal sinus tumor (yolk sac tumor) were identified.

The patient received no post-operative chemotherapy, but eight months later, the tumor recurred and had extended to thoracic level 9 (Fig.1C). The patient underwent partial resection followed by local radiation (45 Gy) and chemotherapy. Although the tumor responded transiently to the salvage therapy, it recurred outside the irradiation field (Th3/Th4) and metastasized to the midbrain (Fig.D, E). The patient died of the disease 25 months after the initial diagnosis.

The recurrent tumor consisted of neuroepithelial tubular structures and loose mesenchymal tissue (Fig. 2E). Cytokeratin CAM5.2 was positive in the neuroepithelial tubules (Fig. 2F).

Patient 2

A four-month-old girl with an unremarkable prenatal and a limited family history presented with abdominal distention, poor feeding and blood in her diaper. Abdominal and pelvic computed tomography scans showed a heterogeneous 6.5 × 6.5 × 5.0 cm mass within the

pelvis and associated high-grade obstruction of the right kidney with bilateral hydronephrosis, right greater than left (Fig. 1F, G). Spine magnetic resonance imaging showed a large presacral mass with heterogenous contrast enhancement. She underwent resection of the pelvic/presacral mass.

Pathologically, the tumor was composed predominantly of immature neuroepithelium in epithelial cords (Fig.3A), clusters of neuroblasts with rare true rosettes (Fig. 3B) and differentiating neurocytic areas in a neuropil background (Fig. 3C). Rare immature cartilage nodules were seen (Fig. 3D). Embryonal rhabdomyo- sarcomatous areas with skeletal muscle differentiation were also present (Fig. 3E,3F). Neither endodermal sinus tumor nor other germ cell patterns were identified.

She was treated with chemotherapy and two tandem auto stem cell transplantations. Subsequently she developed a vaginal embryonal rhabdomyosarcoma (age five years), sarcoma of the right kidney arising in a cystic nephroma (age eight years), papillary thyroid microcarcinoma and nasal chondromesenchymal hamartoma (age eight years) and cystic nephroma of the left kidney (age nine years).

DICER1 sequencing

In Patient 1, two nonsynonymous variants in *DICER1* (c.2233C>T, p.Arg745* and c.5437G>A, p.Glu1813Lys) were detected, with a variant allelic frequency (VAF) of 52.3% and 34.2%, respectively. No other nonsynonymous variation in other genes on the panel was detected. These results were established after the patient's death and germline or family testing was not performed.

Patient 2 underwent germline *DICER1* testing at age eight years. Sequence results showed a pathogenic frameshift variant (c.4407_4410delTTCT, p.Ser 1470 Leufs*19); this variant was also harbored by the patient's father, who has an unremarkable medical history. Somatic *DICER1* sequencing of the tumor performed on tissue from the paraffin block showed the germline *DICER1* variant (VAF: 51%) and a *DICER1* "hotspot" variant (c.5113G>A; p.Glu1705Lys; VAF: 41.4%).

Discussion

Given the age at presentation and the sacrococcygeal location, it is not surprising that these two neoplasms were initially diagnosed as immature teratomas. However, the detection of tumor-associated pathogenic *DICER1* variation in Patient 1 and the occurrence of multiple *DICER1*-related tumors in Patient 2 (and a germline *DICER1* pathogenic variant) promoted re-consideration of the pathology in these two cases. Though primitive neuroepithelial rosettes and tubules were present in both tumors, the predominant pattern was embryonal rhabdomyosarcoma in the absence of the typical spectrum of teratomatous elements or endodermal sinus tumor which are frequent findings in immature teratoma of the sacrococcygeum [8]. Sarcomas including rhabdomyosarcoma are known to occur in germ cell neoplasms, principally in the mediastinum and gonads, but are unknown in infantile sacrococcygeal teratomas to the best of our knowledge [9, 10]. The combination of primitive neuroepithelial tubular profiles, rhabdomyoblastic and cartilaginous nodules in these two

cases are similar to those observed in several of the other *DICER1*-related tumors including ciliary body medulloepithelioma and cervical embryonal rhabdomyosarcoma [3].

The immature or sarcomatous cartilage and embryonal rhabdomyosarcomatous elements are features of pleuropulmonary blastoma types I through III. Primitive neuroepithelial structures and rhabdomyosarcoma are found in pituitary blastoma and heterologous Sertoli-Leydig cell tumor of the ovary, respectively. Neither of these two neoplasms had foci of yolk sac tumor which are often identified as microscopic foci in immature teratomas of the sacrococcygeum. These suggest the present cases are previously unidentified pathological subtype of presacral tumor and a novel *DICER1*-associated tumor.

The International Pleuropulmonary Blastoma /*DICER1* and Ovarian and Testicular Stromal Tumor Registries performed a search of all treating institution and central review diagnoses (search terms: germ cell, teratoma, yolk sac tumor, sacrococcygeal, tumor, seminoma, germinoma) for enrolled individuals with germline *DICER1* pathogenic variation. There were no centrally-reviewed cases of germ cell tumors in either Registry (706 patients from more than 500 families). As the pathological findings of present cases resembles immature teratoma, we then reviewed the published accounts of *DICER1* variation in germ cell tumors. As shown in Table 1, there were numerous tumors with somatic truncating or hotspot variation in *DICER1*, but there were no reports of pathogenic germline *DICER1* variation [4, 11–16]. In addition, the tumors with *DICER1* variation typically do not include detailed pathologic descriptions, and thus we cannot verify with certainty that they are not phenotypic mimics of either known or yet uncharacterized malignant neoplasms. Taken together, we could not find evidence that germ cell tumors are associated with pathogenic germline *DICER1* variation.

Importantly, to date, no reported case has suggested an association between *DICER1* variation and immature teratomas or infantile presacral tumor. Also of note, Patient 2 developed subsequently four *DICER1*-associated neoplasms; this number of the tumors was relatively high as Brenneman et al. reported the mean and median number of lesions in children with pathogenic germline *DICER1* variation as 1.8 and 2.0, respectively [7].

Furthermore, immature teratomas typically are not associated with normal AFP levels and rarely disseminate intracranially, unlike the clinical presentation of Patient 1. [17, 18]. However, metastasis to the central nervous system is the most common site of distant spread by pleuropulmonary blastoma. Patient 1 did not receive chemotherapy after total resection of tumor due to the limited efficacy of chemotherapy against extracranial immature teratoma. In contrast, Patient 2 received intensive chemotherapy and remains in complete remission although the initial tumor was incompletely resected. Therefore, this tumor was aggressive, and the patient may have benefited from adjuvant chemotherapy.

In summary, we present two infantile sacrococcygeal tumors mimicking immature teratoma in two unrelated children (one with germline pathogenic *DICER1* variation) that may be a new subtype of *DICER1*-related infantile tumors. We had not previously seen tumors in this location in *DICER1* carriers in the International Pleuropulmonary Blastoma Registry suggesting they may be one of the rarer tumors associated with *DICER1* pathogenic

variation. We anticipate that an increased use of multi-gene next generation sequencing panels may lead to further expansion of the spectrum of disease associated with *DICER1*. Recognition of a pathogenic germline *DICER1* variant permits cascade genetic testing and potential identification of other family members at increased risk of malignancy. Surveillance guidelines and quantification of neoplasm risk and for *DICER1*-carriers are available [19, 20].

This new entity, which we propose to call *DICER1*-associated presacral malignant teratoid neoplasm, may be difficult to distinguish from immature teratoma, however recognition can facilitate appropriate classification as an aggressive malignancy and will facilitate appropriate genetic counseling, *DICER1* germline variant testing, screening and education.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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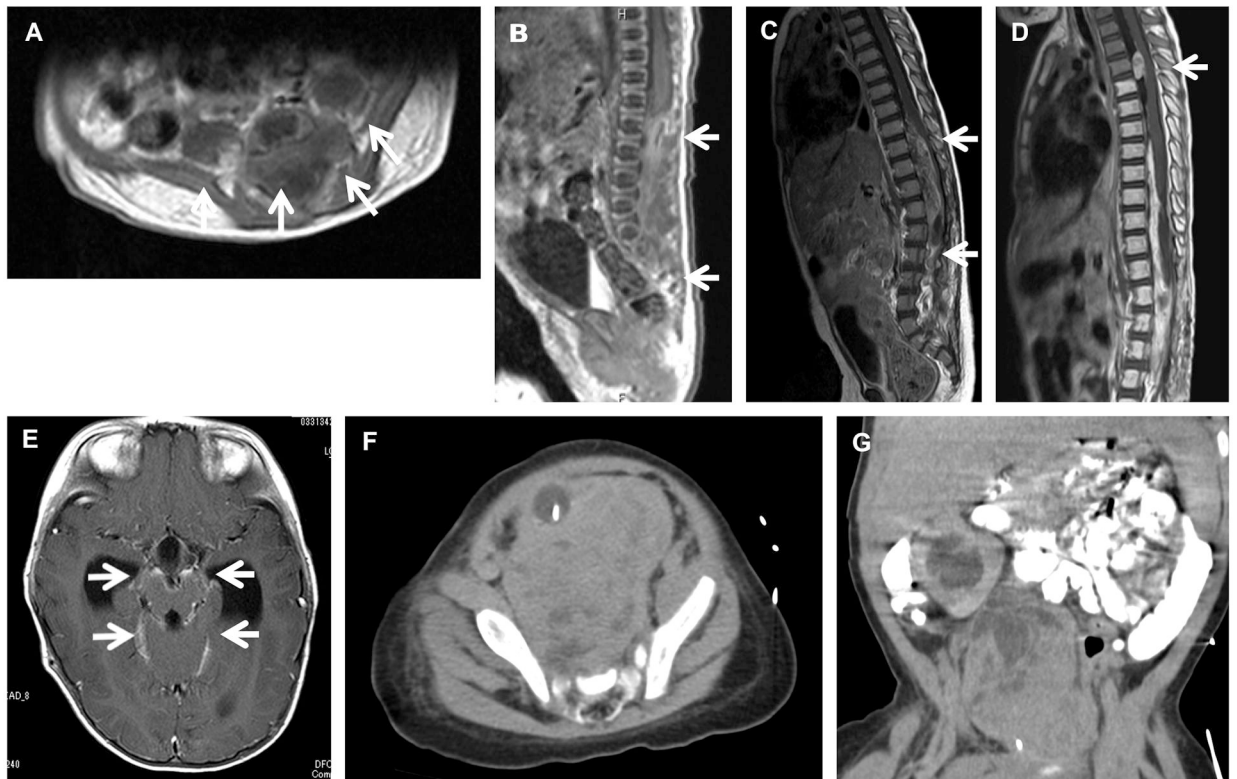


Figure 1.

Radiological findings, with arrow indicating tumor. Gadolinium-enhanced magnetic resonance imaging at first diagnosis (A, B), the first relapse (C), and the second relapse after radiotherapy (D, E) in Patient 1. Patient 2 axial (F) and coronal (G) views from pre-operative computed axial tomography imaging with oral and intravenous contrast showing a heterogenous, paramedian pelvic mass and asymmetric kidneys. There is delayed urinary excretion on the right due to obstruction from the mass. In the axial image (F), the balloon of the urinary catheter is apparent and displaced ventrally and significantly away from the midline.

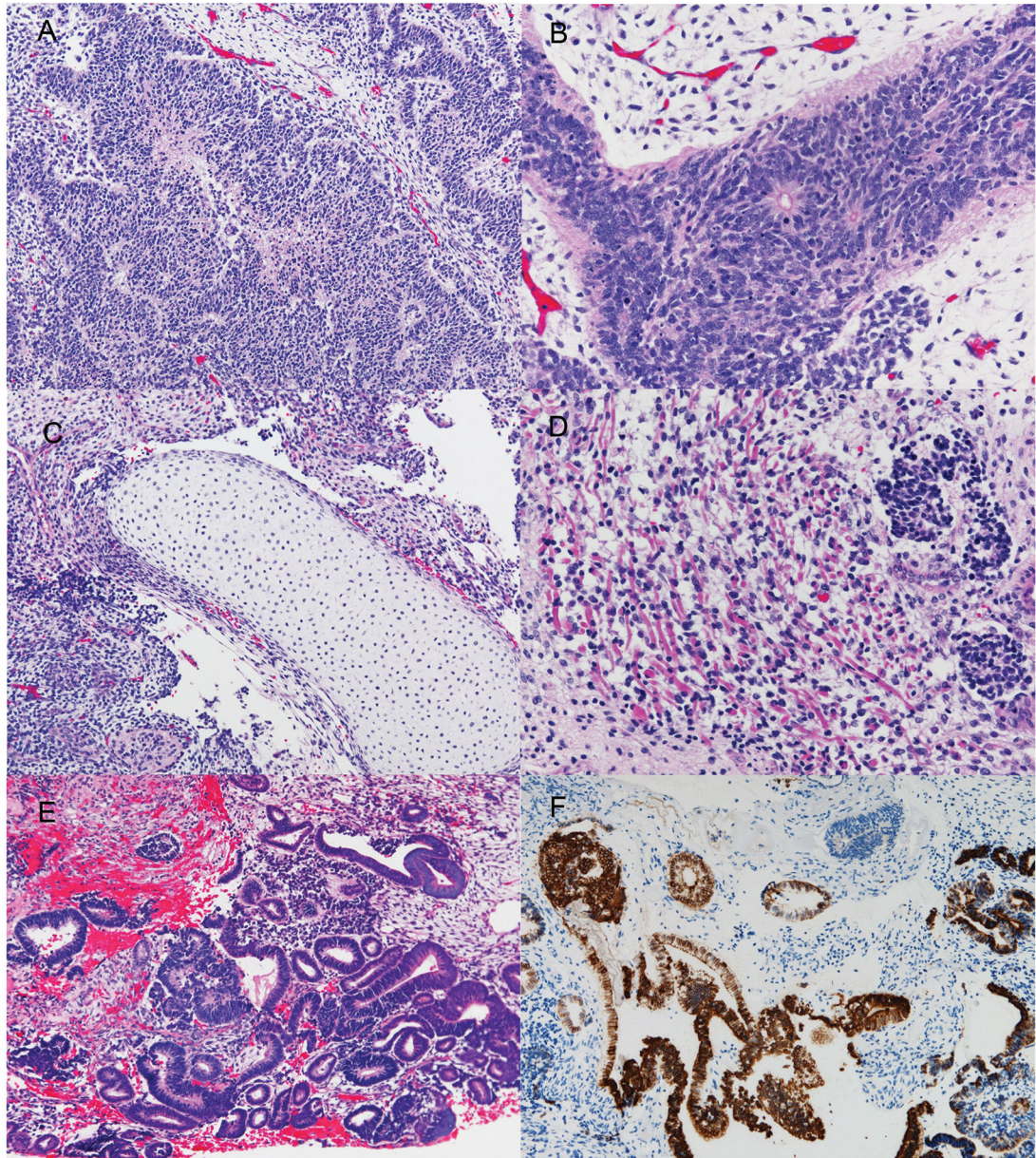


Figure 2.

Microscopic appearance of the multipatterned tumor from Patient 1. The primary tumor from Patient 1 showed immature neuroepithelial components including multilayered rosettes and medulloepithelioma-like component (A, B), and immature mesenchymal tissues, including mature cartilage and skeletal muscle cells (C, D). The recurrent tumor was composed predominantly of neuroepithelial tubular structures in loose mesenchymal tissue (E). These tubules were positive for cytokeratin CAM 5.2 (F). Hematoxylin and eosin (A-E); Anti-CAM 5.2 (F): Original magnification x 100 (A); x 200 (C, E, F), x 400 (B, D).

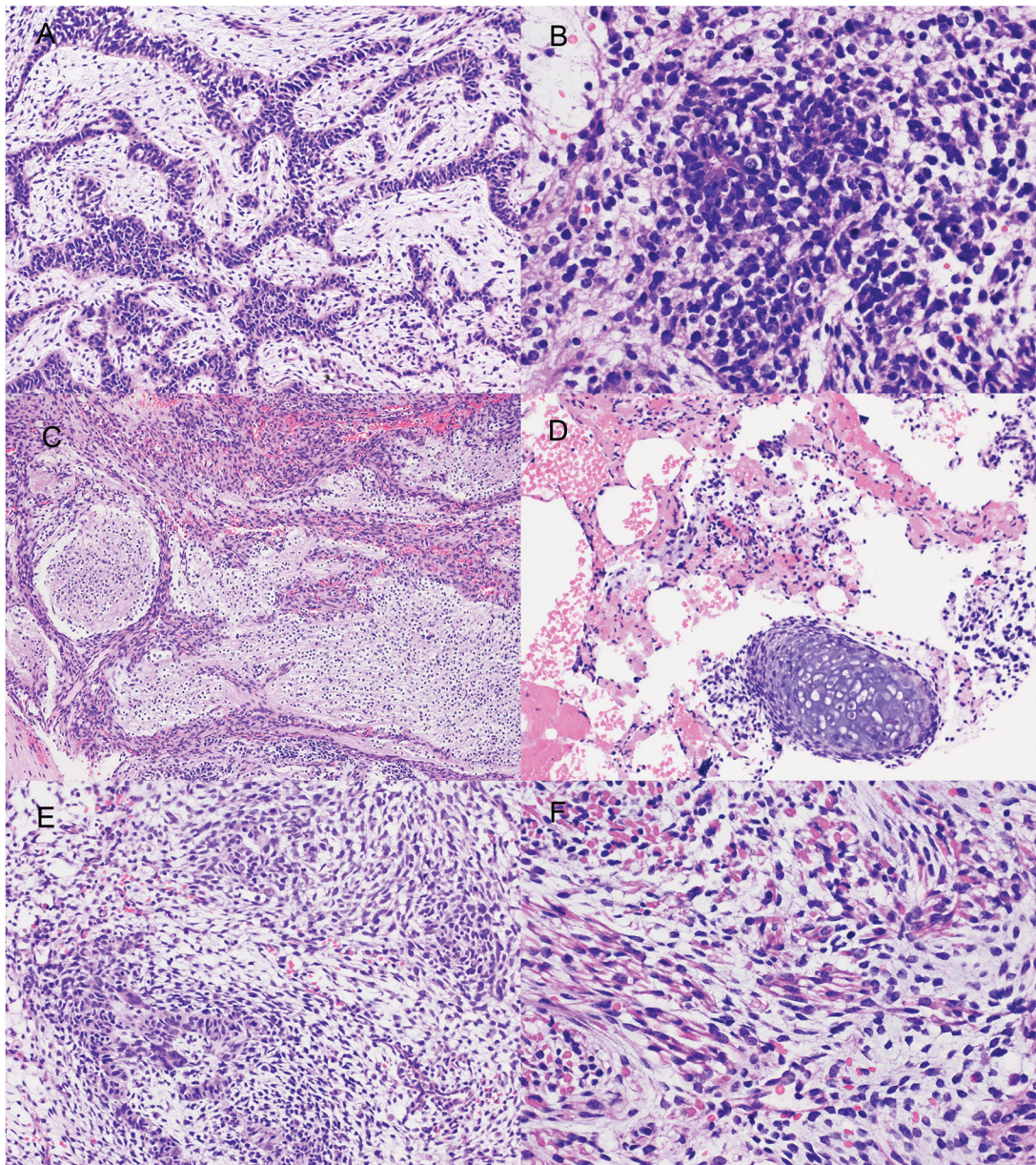


Figure 3. Microscopic appearance of the multipatterned tumor from Patient 2. The tumor from Patient 2 was composed predominantly of immature neuroepithelium in epithelial cords (A), clusters with neuroblasts with rare true rosettes (B) and differentiating neurocytic areas in a neuropil background (C). Rare immature cartilage nodules were seen (D). Embryonal rhabdomyosarcomatous areas with skeletal muscle differentiation were also present (E, F). Hematoxylin and eosin: Original magnification x 200 (A, D, E); x 100 (C), x 400 (B, F).

Table 1.

Published reports of germ cell tumors with *DICER1* variation

| Diagnosis | Demographics (Sex/Age) | <i>DICER1</i> Somatic/Germline | Comment on Histology | Follow-up | Reference |
|----------------------------------------------------------------------------------------------|------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------|
| Sacrococcygeal teratoma with nephroblastoma | Female/3 years | N/A | Composed predominantly of nephroblastomatous tissue; ultrastructural features like Wilms | Alive and well after 12 months | Ward Cancer 1974 |
| Seminoma (1 of 72 in series) | Male/32 years | No data/c.G4740G; p.Q1580H | No data | Alive at 46 years | Stade JMG 2011 |
| Primitive germ-cell tumor: Yolk sac (PGCTYS-01)* | No data | c.G5125A; p.D1709N/ No data | No data | No data | Heravi-Moussavi NEJM 2012 |
| Primitive germ-cell tumor: Yolk sac (PGCTYS-02)* | No data | c.T5127A; p.D1709E and trans c.G5492A; p.Y1831Ter/ No data | No data | No data | Heravi-Moussavi NEJM 2012 |
| Teratoma: Mature [§] | No data | c.G5428T; p.D1810Y/ No data | No data | No data | Heravi-Moussavi NEJM 2012 |
| Testicular germ cell tumor (seminoma) [#] | No data | p.R1725Q/ No data | No data | No data | De Boer BMC Research Notes 2012 |
| Mixed germ cell tumor (yolk sac tumor/ immature teratoma) [^] | Female/27 years | c.G5428T; p.D1810Y/ No data | No data | No data | Witkowski BIC 2013 |
| Mixed gonadoblastoma/dysgerminoma [^] | Female/15 years | c.A5429G; p.E1788fs*41/ No data | No data | No data | Witkowski BIC 2013 |
| Mixed germ cell tumor (dysgerminoma/ yolk sac tumor) [^] | Female/9 years | c.A5438G; p.E1788fs*41/ No data | No data | No data | Witkowski BIC 2013 |
| Mixed germ cell tumor (embryonal carcinoma/ immature teratoma/ choriocarcinoma) [^] | Male/ 12 years | c.A5438G; p.E1788fs*41/ No data | No data | No data | Witkowski BIC 2013 |
| Yolk sac tumor [^] | Male/ 1 year | c.A5438G; p.E1788fs*41/ No data | No data | No data | Witkowski BIC 2013 |
| Familial testicular germ cell tumors | 43 probands | Numerous likely non-pathogenic germline variants | No data | No data | Sabbaghian BMC Research Notes 2013 |
| Malignant thyroid teratoma | Female/59 years | c.A5438G; p.E1813G [%] / No data | Post-chemotherapy pathology showed residual teratoma with extensive hyalinization, necrosis, dystrophic calcification, chronic inflammation and pigment-laden histiocytes consistent with treatment effects | Alive at 4-year follow-up | Rabinowitz Thyroid 2017 |

* Of 15 yolk-sac tumors sequenced, two harbored somatic *DICER1* variation§ Of 5 immature and 9 mature teratomas sequenced, one mature teratoma harbored somatic *DICER1* variation

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A somatic *DICER1* variant found in 96 TGCT tumors.

% This somatic *DICER1* variant was observed in 56% of reads; no copy-number changes were observed. Two *TP53* variants were also observed (c.G743A: p.R248Q and c.376_splice:p.Y126_splice) and an *NF1* variant (c.A3160C: p.N1054H) in 6–8% of reads, suggesting a subclonal tumor population.

^ Data on five tumors reported in Table 3 of Witkowski 2013. A total of 99 ovarian germ cell tumors and 19 testicular germ cell tumors were sequenced resulting in 5/118 (4.2%) with a somatic *DICER1* variant. Germline DNA was available for only 5 tumors (not specified) and did not show *DICER1* variation.