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Underreporting *of SMARCB1* alteration by clinical sequencing: Integrative patho-genomic analysis captured *SMARCB1*/INI-1 deficiency in a vulvar yolk sac tumor

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1. Introduction

SMARCB1 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1) encodes a protein called INI1, a component of the SWI/SNF chromatin remodeling complex (Masliah-Planchon et al., 2015). The INI1-containing SWI/SNF complex modifies chromatin structure to regulate gene transcription modulating stemness, differentiation, and proliferation (Masliah-Planchon et al., 2015). In humans, somatic inactivation of *SMARCB1,* leading to functional loss of INI1, is found in pediatric and adult tumors, including epithelioid sarcoma, atypical teratoid/rhabdoid tumors, sinonasal carcinoma, and renal cell cancer (Masliah-Planchon et al., 2015; Lee et al., 2012; Bourdeaut et al., 2007; Sullivan et al., 2013; Agaimy et al., 2017; Kiyozawa et al., 2022). In the gynecologic tract, *SMARCB1*/INI1 deficiency is found in a subset of high-grade ovarian, uterine, cervical, and vulvar tumors (Kolin et al., 2022; Folpe et al., 2015; Kobel et al., 2018; McCluggage and Stewart, 2021; Kolin et al., 2020). The spectrum of SMARCB-1deficient vulvar tumors include epithelioid sarcoma, myoepithelial carcinoma, vulvar yolk sac tumor, and myoepithelioma-like tumors of the vulvar region (Yoshida et al., 2015). A key feature of this tumor class is the proliferation of rhabdoid cells, characterized by large epithelioid cells with prominent nucleoli, uncondensed chromatin, and cytoplasmic inclusions of intermediate filament whorls (Masliah-Planchon et al., 2015) (Fig. 1). Occasionally, some *SMARCB1*/INI1-deficient tumors show dedifferentiation and acquisition of primitive yolk sac tumor (YST) features (Hazir et al., 2022; Nakano et al., 2021; Ohe et al., 2018). Timely identification of *SMARCB1*/INI1 deficiency is paramount, since these malignancies are aggressive and resistant to conventional chemotherapy, and should be referred for precision oncology clinical trials.

In clinical settings, *SMARCB1*/INI1 deficient tumors are diagnosed by either next generation sequencing (NGS) or immunohistochemistry (IHC). However, due to technical limitation of NGS and interlaboratory variability in sequencing methodologies and analytical pipelines, *SMARCB1* deficiency due to somatic copy number variations (SCNV) may be underreported.

Herein, we report a case of a young woman with an aggressive vulvar cancer, and a delay in recognizing its association with *SMARCB1*/INI1 deficiency. This index case illustrates that a combination of careful pathology review, understanding that SCNV as a common genomic alteration leading to *SMARCB1*/INI1 deficiency, and familiarity with NGS assay limitations, improves the identification of *SMARCB1*/INI1 deficient neoplasms. Further, the occurrence of INI1-deficient vulvar yolk sac tumor in the context of germline *LZTR1* mutation is discussed.

2. Case report

A 26-year-old woman with no past medical history presented with a painful vulvar mass. A biopsy was performed prior to the first vulvectomy surgery which suggested a vulvar yolk sac tumor. PET/CT scan showed a $7.3 \times 7.1 \times 3.9$ cm lobulated right vulvar soft tissue mass, with disease isolated to the pelvis with no extrapelvic metastasis. A month later, she then underwent a right radical vulvectomy with a right groin lymph node dissection, which yielded 7 of 7 lymph nodes with metastasis. The intraoperative findings included a 12 cm right-sided mass protruding through the anterior right labium majus and replacing about two-thirds of the mons. There were palpable lymph nodes adjacent to the mass. The surgeon was able to achieve a primary closure without

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needing a flap. The surgeon noted the surgery to be more challenging than a typical radical partial vulvectomy, due to the extremely large size of the mass and the complexity of reconstruction. Her post-operative course was reportedly uncomplicated. Her surgical pathology showed a 7.3 cm vulvar yolk sac tumor, with all seven sampled lymph nodes positive for metastasis. Her postoperative serum alpha fetal protein (AF) level was 31.1 ng/mL (reference range: 0.0–4.7 ng/mL). She then received 4 cycles of bleomycin, etoposide and cisplatin (BEP), and developed debilitating leg cramp. Six months later, her imaging showed multiple hypermetabolic nodules in the lung, lower abdominal wall and vulva. She then transferred her care to our tertiary cancer center. She was put on ifosamide, carboplatin, etoposide (ICE) regimen for 2 cycles. Upon radiologic and serologic progression (AFP = 77.1 ng/mL), she was switched to gemcitabine and docetaxel for 1 cycle.

Prior to coming to our institution for a second opinion, the patient had consulted with two other institutions. Her prior oncologists had ordered NGS assays at two separate CLIA-accredited commercial laboratories. Laboratory 1 employed a 523-cancer-relevant gene panel analysis and sequenced the initial vulvectomy specimen. Laboratory 2 employed tumor-only whole exome sequencing analysis (~22,000 genes) and sequenced the groin recurrence tumor. The two laboratories reported no clinically actionable alterations. Both laboratories reported a low tumor mutation burden (TMB; 2 mutations/megabase). Later, her pathology slides were reviewed by a gynecologic subspecialty pathologist. The tumor showed rhabdoid morphology. This prompted IHC workup for INI1, which was lost in the tumor cells from her original vulvectomy and recurrence specimens. In addition, the tumor demonstrated an immunoprofile of primitive/germ cell-like differentiation, including alpha fetal protein (AFP) and SALL4 expression. Fig. 1 summarizes the pathologic findings of her vulvar tumor. To explore the possibility of underreporting of *SMARCB1* mutation, her most recent vulvar recurrence specimen was sent to Laboratory 3, which employed paired tumor-normal whole exome sequencing. Laboratory 3 reported biallelic loss of *SMARCB1*. No other mutations were identified. The TMB was again low (1 mutation/megabase). Table 1 summarizes the key findings from all 3 laboratories. Eventually, approximately one year later since her initial diagnosis, she underwent germline testing, which revealed a mutation in *LZTR1* (c.481 C > T). Also,y, she enrolled into a

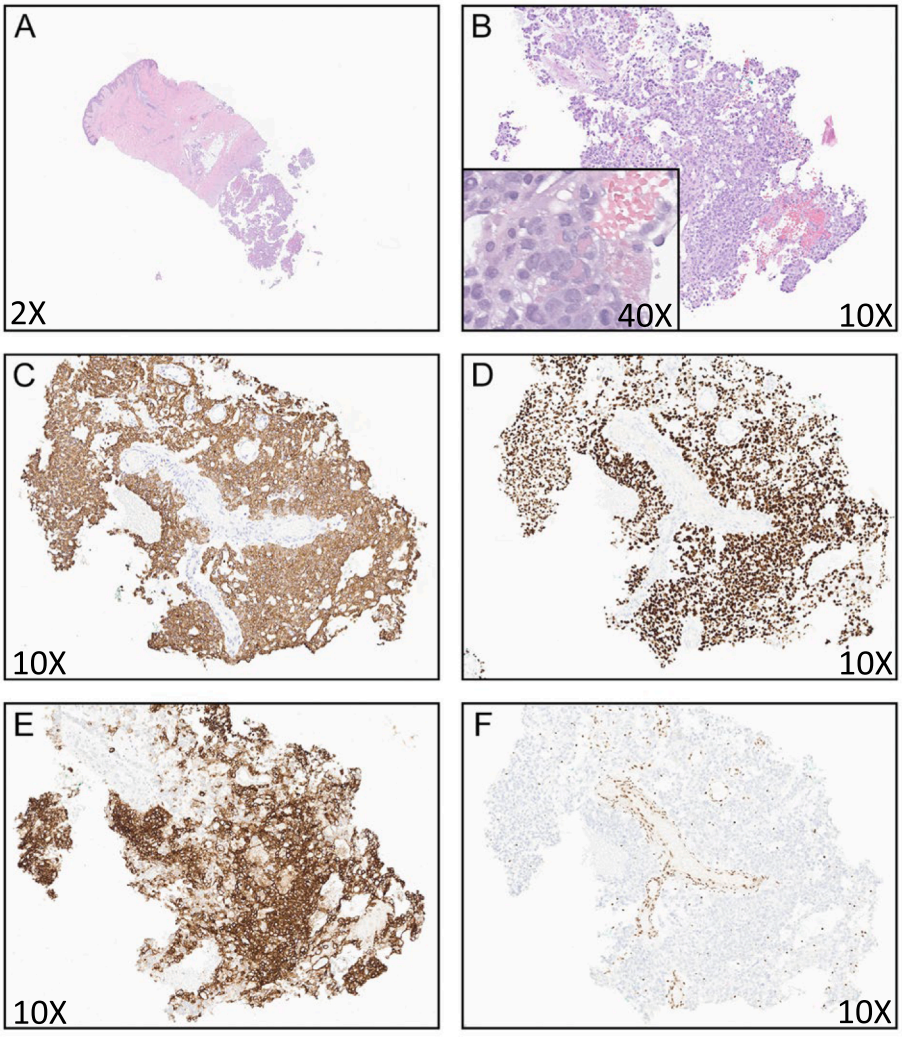

Fig. 1. Photomicrographs of *SMARCB1*/INI1-deficient vulvar yolk sac tumor. (A): Scanning magnification of hematoxylin and eosin-stained slide showing a solid proliferation of epithelioid tumor cells in the deep dermal/subcutaneous layer of the vulva. (B): Higher magnification view of the tumor cells. The inset demonstrates the classic morphology of *SMARCB1*/INI-deficient tumors, characterized by rhabdoid morphology of the individual neoplastic cells, with occasional intracytoplasmic pink inclusions which represent intermediate filament whorls. (C-F): Immunoprofile of the vulvar yolk sac tumor. Tumor cells are strongly positive for keratin marker pan-cytokeratin (C), primitive/germ cell marker SALL4 (D), and yolk sac tumor specific marker glypican (E). The tumor cells demonstrate loss of INI1 expression (F), supportive of biallelic inactivation of *SMARCB1*. Note the internal positive control, where the blood vessels show retained INI1 expression in the nuclei of endothelial cells. Microscope objective's magnification is represented in the left or right lower corners of the image box. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of the molecular assays, specimen characteristics, *SMARCB1* molecular status, and INI1 immunohistochemistry status.

Laboratory	Sequencing method	Tumor sample	Tumor purity (germline *LZTR1* mutation MAF)	*SMARCB1* status per report	INI1 IHC result
1	Panel based NGS (523genes), tumor only	Original vulvectomy specimen	>90 % (48 %)	Normal	Loss
2	Whole exome NGS, tumor only	Groin recurrence	>90 % (49 %)	Indeterminant result	Loss
3	Whole exome NGS, tumor and paired normal patient blood	Vulvar recurrence	>90 % (49 %)	Biallelic loss	Loss

Abbreviations: NGS = Next generation sequencing. IHC = Immunohistochemistry. MAF = Mean allelic frequency.

precision clinical trial targeting the SWI/SNF pathway and received an experimental drug - a degradation activating compound degrader of BRD9 (bromodomain-containing protein 9) - which is showed preclinical activity in both *in vivo* and *in vitro* models of SMARCB1-null solid tumors. In her first two months on clinical trial, she reported symptomatic improvement with softening of her groin tumor. Her serum AFP level nadired to 19.1 ng/mL. Unfortunately, after 3 months on clinical trial she developed progressive disease in her lower abdominal wall, vulva, and new pulmonary metastases. She came off of clinical trial and was restarted on gemcitabine and docetaxel for 4 cycles, and tolerated this regimen without significant side effects. While on this regimen, her PET/CT scans showed partial treatment response, with resolution of her pulmonary metastases and decrease in size of her vulvar mass. However, 6 months later she was found to have radiologic and biochemical progression, now presenting an enlarging groin mass with elevated serum AFP (1003.2 ng/mL). At the latest follow-up, she opted to undergo radical tumor debulking surgery.

3. Discussion

We present a case of a young woman with *SMARCB1*/INI1-deficient vulvar neoplasm with YST differentiation. Pathogenic *SMARCB1* mutation was underreported by two different CLIA-certified commercial molecular sequencing laboratories. To improve identification of *SMARCB1*/INI1-deficient neoplasm, we propose the following strategy: First, careful pathology slide review and detection of rhabdoid cells should raise the possibility of *SMARCB1*/INI1 deficiency. Second, INI1 IHC is a useful complementary test to exclude clinical suspicion of *SMARCB1* deficiency in the context of negative molecular reporting. Third, knowledge of potential underreporting of SMARCB1 mutation would avoid underdiagnosis.

An array of genomic alterations lead to pathogenic mutations, including base substitution, frameshift, insertion and deletion, genomic rearrangement, and SCNV (Vogelstein et al., 2013). *SMARCB1*/INI1 deficient tumors are mostly driven by biallelic loss of *SMARCB1* gene, a SCNV event (Masliah-Planchon et al., 2015). Recognition of testing nonuniformity across various CLIA-accredited molecular laboratories is crucial to inform the need for additional workup (e.g. IHC or retesting using a different NGS laboratory).

How do interlaboratory differences contribute to variances in detecting SCNV? The short answer is that laboratories are not equally adept at overcoming technical and biological challenges of detecting absolute copy number variation in solid tumors. Biallelic inactivation of *SMARCB1* is mediated through recurrent genomics events including whole-gene deletions, complex intragenic deletions or duplications, and splice-site mutations (Masliah-Planchon et al., 2015; Sevenet et al., 1999). These structural variations pose detection challenges in clinical tumor profiling assays using targeted NGS, secondary to inherent technological limitations such as short read sequencing, use of bait selection, coverage biases from non-uniform target amplification, mapping ambiguity, and mathematical assumptions made during bioinformatic calculations (Chen et al., 2013; Ross et al., 2013; Ma et al., 2019). Indeed, under-detection of *BRCA1/2* multi-megabase structural variants by some NGS methods has been previously recognized, and alternative bioinformatic analytical pipelines have been proposed to mitigate these events (Ewing et al., 2021). Biologic challenges for SCNV calculation include tumor aneuploidy, tumor purity and contamination by bystander normal cells, and intratumoral heterogeneity (Gusnanto et al., 2012).

In our case, interlaboratory variation is likely the reason for discordant reporting of *SMARCB1* mutational status by these three independent laboratories, which all employed different NGS methodologies (Table 1). While it is possible that biologic variation in the tested specimens (vulvectomy and recurrence tumors) could have contributed to discordant reporting, however all three specimens contained high tumor purity (>90 % tumor cellularity); similar 49 % allelic frequency of patient's known germline *LZTR1* (~49 %), and loss of INI1 protein expression, lending no support for significant intratumoral heterogeneity or low tumor purity as biological confounders. From a technical standpoint, there are important methodologic differences amongst the three laboratories. For example, Laboratory 1 used a gene panel-based approach while Laboratory 2 and 3 employed whole-exome sequencing approach, which introduce differences in target space and sequencing context, gene coverage, GC content, and mappability of reads, which ultimately could lead to disparities in quantifying copy number information using read counting approach (Zhao et al., 2013). Another major difference between the three laboratories is they used different bioinformatic pipelines to calculate SCNV, and used different input sequencing data and reference samples in their calculation (Table 1). For example, Laboratory 3 shows convincing *SMARCB1* gene deletion by calculating the sequence coverage differences between tumor and patient's normal specimen at specific intervals of *SMARCB1* exons, and the fold changes on the logarithmic scale (log2fc) is interpreted using laboratory's prespecified cutoffs for classifying gene amplification or loss (Fig. 2). In contrast, Laboratory 2 compares the tumor copy number profile to a pool of reference samples, resulting in no reporting of *SMARCB1* gene mutation status. Interestingly, Laboratory 2 ultimately classifies its finding as gene tested with indeterminant results. Eventually, re-review of the case with Laboratory 2 showed possible *SMARCB1* deletion event. However, the alteration did not meet Laboratory 2's established reporting threshold. Concurrent whole transcriptome expression analysis revealed low *SMARCB1* expression (3transcriptspermillionmolecules) by Laboratory 2, corroborating with the impression of *SMARCB1* loss. Laboratory 1 utilized panel-based assay and did not detect evidence of *SMARCB1* deletion upon re-review of the case.

A subset of *SMARCB1*/INI1-deficient tumors exhibit morphologic and immunohistochemical evidence of YST-like phenotype. Whether or not these tumors are germ cells versus somatically derived tumors with yolk sac differentiation is an important clinical question with therapeutic implications. If these *SMARCB1*/INI1-deficient tumors are truly germ cell tumors, they are expected to respond to germ cell-targeting therapy. On the contrary, patients in prior reported cases series, and in our case, did not show response to YST chemoregimen (Kolin et al., 2022). Hence, the lack of tumor response to YST chemoregimen supports that *SMARCB1*/INI1-deficient tumors with YST features are not identical to germ-cell YST. This observation is consistent with a recent comparative genomic study, which showed no similarity between the two entities (Kolin et al., 2022). The mechanism underlying primitive YST-differentiation in *SMARCB1*/INI-deficient tumors is unknown, but may

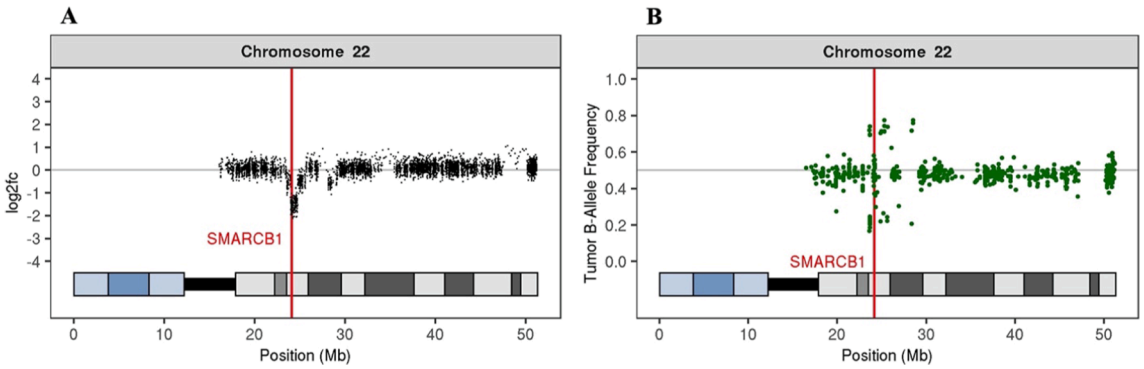

Fig. 2. Copy number variation (A) and B-allele frequency (B) plots of chromosome 22q analysis by Laboratory 3. The analysis shows biallelic loss of *SMARCB1*.

be related to *SMARCB1*'s role in regulating differentiation through chromatin remodeling and transcriptional regulation. In mouse embryonic stem cells, *SMARCB1* deficiency caused impaired differentiation during embryonic development *in vivo* with retention of pluripotent state (Sakakura et al., 2019).

Lastly, another unique aspect of this case report is the repeated number of NGS tests our patient had received, which produced significant financial toxicity to the patient and to our healthcare system. We do not know if our patient's insurance had paid for all three NGS tests. However, our patient is a highly educated individual, and had sought care at two other institutions prior to establishing care at our institution. From chart review, it appeared that the first two NGS tests were ordered by two different oncologists at two differential institutions. It is not clear if the second oncologist was aware of the existence of the first molecular report. The third NGS was requested at our institution, given the discordant molecular results reported by the first two NGS tests, and in the context of our high index of suspicion for SMARCB1 gene deletion event in the tumor cells. We chose this specific testing platform (paired tumor-normal whole exome sequencing analysis), which is technically more sensitive than targeted NGS panel without normal control to assess somatic copy number variations (SCNVs). This underscores the need for clinicians in the Precision Oncology era to be familiar with various NGS assays, and the assay strengths and weaknesses. Furthermore, the lack of electronic integration of NGS test results from different commercial laboratories may contribute to wasteful, repeated NGS testing. This scenario is more likely to occur if the patients seek second opinions from multiple oncologists at various institutions, each may have their preferential commercial NGS assays.

To our knowledge, we are first to report the occurrence of *SMARCB1*/INI-1deficient vulvar yolk sac tumor in the context of *LZTR1* germline mutation. *LZTR1* inactivating mutation, occurring in splice-site at codon 217, is associated with Noonan Syndrome, glioblastoma, and schwannomatosis (Bigenzahn et al., 2018; Steklov et al., 2018). Loss of *LZTR1* function has been shown to increase RAS signaling and phosphorylation of MEK1/MEK2 and ERK1/ERR2 pathways, and reduced sensitivity to tyrosine kinase inhibitors. It is unclear if our patient's germline *LZTR1* genotype (c.481 C > T) and SMARCB1-deficiency acted cooperatively to cause this rare vulvar tumor in this patient. Of note, our patient has no medical history of *LZTR1*-associated diseases, where the mutation is occurring on amino acid position 161 and the variant not reported on the catalogue of somatic mutations in cancer (COSMIC) website. Prospective data collection of germline genotype in women with *SMARCB1*/INI1-deficient gynecologic malignancies is needed to clarify this potential association.

In summary, underdiagnosis of *SMARCB1*/INI-1 deficient tumors can be mitigated by integrative pathogenomic analysis. This includes careful pathology review for presence of rhabdoid cells, use of INI-1 IHC to demonstrate protein loss, and awareness that NGS may underreport *SMARCB1* mutations. *SMARCB1*/INI1-deficient neoplasms are aggressive, occasionally showing primitive differentiation and acquisition of YST phenotype, and showing minimal response to conventional chemotherapy. Early enrollment into precision oncology clinical trials may help increase therapy options.

Ethics statement and acknowledgement of research support

We would like to thank the patient for her consent to publish this case report, including images. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. This study was approved by the COH's review board IRB# 22308 and #07047. The City of Hope Women's Cancers Program and Circle 1500 provided funding. CW was also supported by the National Cancer Institute of the National Institutes of Health K12CA001727 (PI Dr. Mortimer).

CRediT authorship contribution statement

Christina H. Wei: Conceptualization, Investigation, Formal analysis, Resources, Data curation, Writing – original draft, Funding acquisition. **Edward Wang:** Conceptualization, Writing – review & editing. **Evita Sadimin:** Writing – review & editing, Resources, Visualization. **Lorna Rodriguez-Rodriguez:** Conceptualization, Resources, Writing – review & editing. **Mark Agulnik:** Conceptualization, Resources, Writing – review & editing. **Janet Yoon:** Conceptualization, Resources, Writing – review & editing. **Janine LoBello:** Conceptualization, Writing – review & editing, Formal analysis. **Szabolcs Szelinger:** Conceptualization, Writing – original draft, Formal analysis. **Clarke Anderson:** Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

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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