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Metastatic Granular Cell Tumor of the Vulva With CHEK2 Mutation: A Case Report and Molecular Insights

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Abstract: Granular cell tumors (GCTs) are rare neoplasms, typically of Schwannian origin, with generally a benign and indolent clinical behavior. However, a small subset exhibits malignant behavior, often without clear histologic features. We report a rare case of a vulvar granular cell tumor in a 21-yr-old woman with subsequent pulmonary metastasis. The patient presented with a slowly growing vulvar nodule and a subcutaneous lesion on the left flank. Imaging studies revealed residual disease in the vulva and a suspicious lung nodule, both of which were surgically resected. Histopathologic examination confirmed features consistent with granular cell tumor in both primary and metastatic sites, despite the absence of cytologic atypia, necrosis, or elevated mitotic activity. Immunohistochemistry revealed positivity for S100, CD68, NSE, and inhibin, with a low Ki-67 index (< 1%). Next-generation sequencing identified a CHEK2 p.I200T mutation in both lesions, suggesting a shared clonal origin. This variant lies within the kinase domain of CHK2, a key mediator of the DNA damage response, and is of uncertain but potentially pathogenic significance. No microsatellite instability or homologous recombination deficiency was observed. This case highlights the diagnostic challenges in GCTs, particularly in distinguishing benign from malignant forms in the absence of classic histologic criteria. The presence of metastasis remains the most definitive indicator of malignancy. Our findings underscore the importance of integrating molecular profiling into the diagnostic and prognostic workup of GCTs and raise the question about the potential role of CHEK2 alterations as additional molecular determinants of aggressiveness beyond conventional histology. Long-term follow-up is warranted given the unpredictable clinical behavior of malignant GCTs.

Key Words: Granular cell tumor, Vulvar neoplasm, Pulmonary metastasis, CHEK2 mutation, Malignant soft, Tissue tumor

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Granular cell tumors (GCTs) were first described in 1926 by the Russian pathologist Abrikossoff as rare neoplasms thought to originate from Schwann cells, characterized by distinct pathologic features.[1–3] More recently, a subset of so-called "non-neural" granular cell tumors lacking S100 protein expression has been identified. Unlike their neural counterparts, these tumors are negative for SOX10 and other Schwann cell markers and are thought to arise from alternative mesenchymal or histiocytic lineages[1–3]. Although uncommon, GCTs can arise in a wide range of anatomic sites, most frequently involving the skin, oral cavity, gastrointestinal tract, and subcutaneous tissues. They have also been reported in less typical locations such as the breast, bladder, central nervous system, respiratory tract, and genitourinary system.[1–3] GCTs can occur at any age and in both sexes,

though they are most often diagnosed in women between the fourth and sixth decades of life.[4,5] Clinically, they usually present as solitary, painless nodules measuring < 3 to 4 cm and are often discovered incidentally[6]. While typically solitary, multiple lesions may be present in ~7% to 29% of cases.[5] Most GCTs follow an indolent clinical course; however, a small proportion (1%–2%) may exhibit malignant behavior, defined by histologic criteria or the presence of metastases.[7] These malignant forms are associated with a poor prognosis and limited therapeutic options beyond surgical resection.[7] Herein, we report a well-documented case of a granular cell tumor of the vulva with pulmonary metastasis. We provide a detailed analysis of its molecular and histopathologic features and critically review the diagnostic criteria for malignancy proposed in the literature.

CLINICAL HISTORY

A 21-yr-old woman presented with a slowly enlarging nodule on the left labium major, first noted 5 yr earlier. Her medical history included right nephrectomy, adjuvant chemotherapy and radiotherapy, and autologous stem cell transplantation for stage IV nephroblastoma in 2010, followed by a diagnosis of nodular hyperplasia of the liver in 2017. She underwent a partial vulvectomy at an outside institution, where histopathology revealed a granular cell tumor (GCT) with involvement of the surgical margins. The diagnosis was confirmed upon histologic review at our center. Postoperative examination revealed a raised lesion with micropapillary features at the surgical site, suggestive of residual disease. In addition, a firm, mobile, 2 cm subcutaneous nodule was noted on the left flank. Pelvic MRI showed a 35×15×8 mm T2-isointense lesion in the anterior vulva extending toward the glans clitoris, separated from surrounding tissues by a clear cleavage plane. Based on these findings, a completion vulvectomy with clitoral preservation and excision of the flank nodule was performed. At grossing, a nodular firm mass of 37 mm, yellow with a finely granular texture at the cut surface, has been observed.

Restaging CT identified a 13×9 mm peri-fissural pulmonary nodule in the left lingular segment and a 12×7 mm left hilar lymph node. Both lesions remained morphologically stable on comparison with previous imaging. Subsequent PET scan demonstrated increased FDG uptake (SUVmax 4.6) in both sites, raising concern for malignancy. (Fig. 1) Following multidisciplinary evaluation, the patient underwent uniportal video-assisted thoracoscopic surgery (U-VATS), including lingular wedge resection, multiple pleural biopsies, and diaphragmatic biopsy.

A single 3-cm incision was made at the fifth intercostal space along the mid-axillary line. Intraoperative

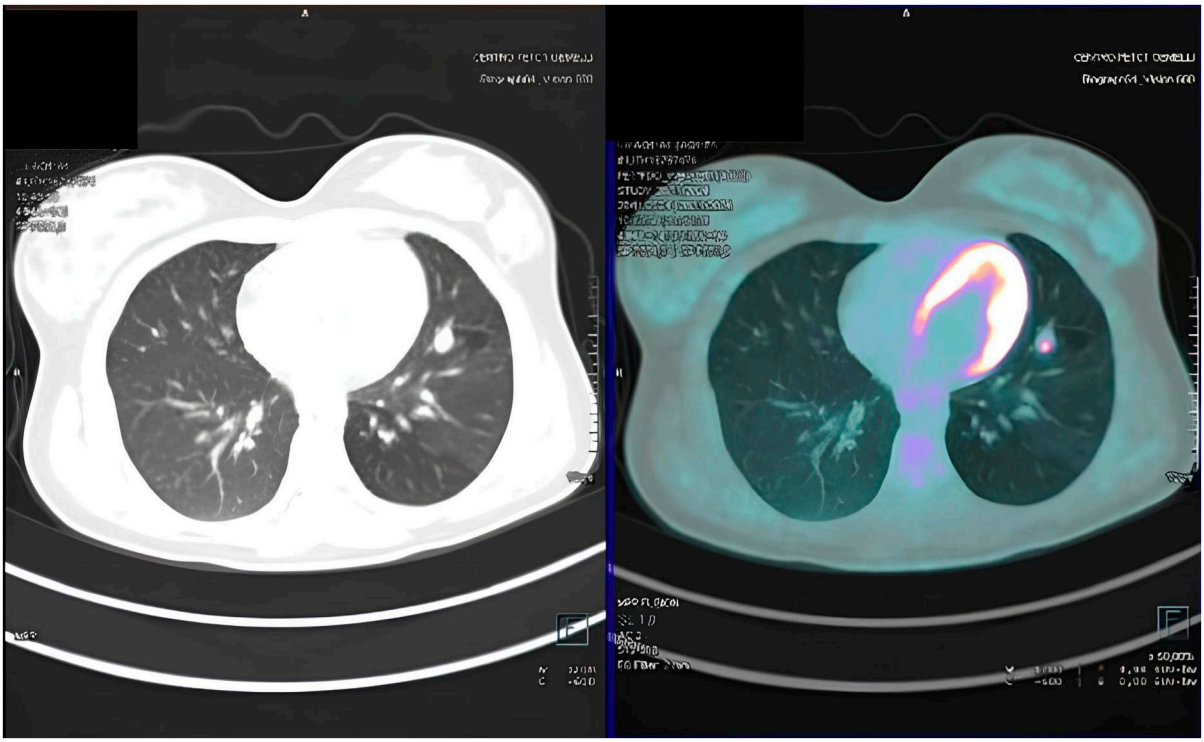

FIGURE 1. CT scan revealed a 13×9 mm peri-fissural nodular lesion in the lingular segment of the left lung, along with a l2×7 mm left hilar lymph node. PET showed increased metabolic activity in both the lingular nodule (SUVmax 4.6) and the left hilar lymph node.

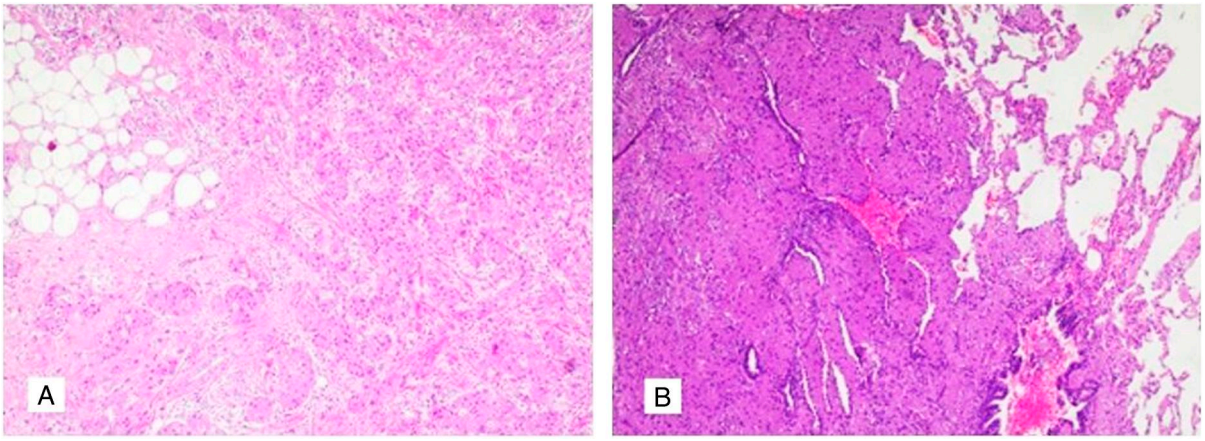

FIGURE 2. (A) Neoplastic cells, arranged in nests and cords infiltrated the vulvar dermis, hypodermis, perivulvar soft tissues, and (B) lung parenchyma (40×).

exploration confirmed the lingular lesion, and 2 additional nodules were identified in the costophrenic angles and biopsied. Frozen section of the lingular nodule showed a proliferation of mesenchymal-like cells, prompting an extended wedge resection to ensure clear margins. Biopsies of pleural and diaphragmatic nodules revealed chronic pleuritis, granulomatous inflammation, and reactive mesothelial proliferation. A 28-Fr chest drain was placed through the same incision at the end of the procedure.

HISTOPATHOLOGIC FINDINGS

Microscopically, the neoplastic cells, arranged in nests and cords infiltrated the vulvar dermis, hypodermis, perivulvar soft tissues, and lung parenchyma (Fig. 2). Importantly, the morphologic features were consistent across all specimens: the initial partial vulvectomy, the subsequent completion resection, and the pulmonary metastasis. In each site, the tumor demonstrated a poorly circumscribed proliferation of epithelioid cells with abundant eosinophilic granular cytoplasm, centrally located vesicular nuclei, and occasional prominent nucleoli (Fig. 3).

The tumor cells were arranged in nests and cords, separated by dense collagenous stroma, and exhibited a syncytial growth pattern. No evidence of necrosis, mitotic figures, lymphovascular invasion, or significant spindle cell morphology was identified.

Immunohistochemically, the tumor cells were diffusely positive for S100, CD68, neuron-specific enolase (NSE), vimentin, and inhibin, while negative for cytokeratin AE1/AE3 (Fig. 4). The Ki-67 proliferation index was low, with nuclear positivity observed in fewer than 1% of tumor cells.

MOLECULAR FINDINGS

Molecular analysis was conducted on both the vulvar primary lesion and the pulmonary metastatic lesion. NGS analysis was carried out by adopting OncoDEEP DNA Kit Comprehensive Genomic Panel (CGP), a 409-gene panel covering key cancer-related pathways, and then sequencing on Illumina NextSeq. 550Dx. Data were analyzed using Mercury and OncoKDM software (CE-IVD certified). A point mutation p.I200T in the *CHEK2* gene (p.I200T, VAF of 48,3%) was identified in both the primary vulvar tumor and the pulmonary metastasis. The *CHEK2* c.599T > C (p.Ile200Thr) variant is a missense substitution of isoleucine with threonine at codon 200, located within the kinase domain of the CHK2 protein, a functionally critical region involved in DNA damage signalling.[8] According to ClinVar (Variation ID: 5591), this variant has conflicting interpretations of pathogenicity, ranging from uncertain significance to likely pathogenic. The comparable allele frequency observed in both lesions suggests a possible germline origin. *CHEK2*

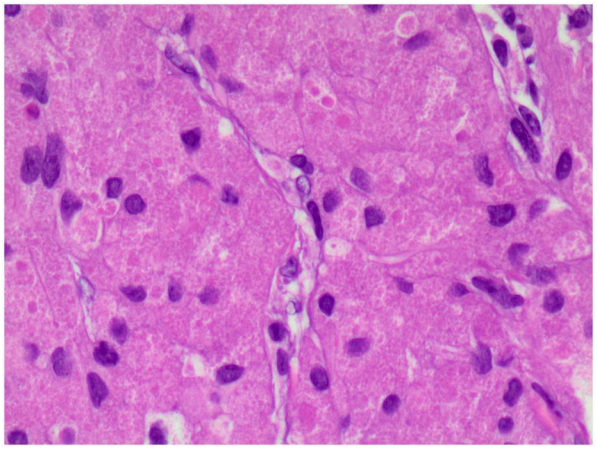

FIGURE 3. Epithelioid cells with abundant eosinophilic granular cytoplasm, centrally located vesicular nuclei, and occasionally prominent nucleoli (400×).

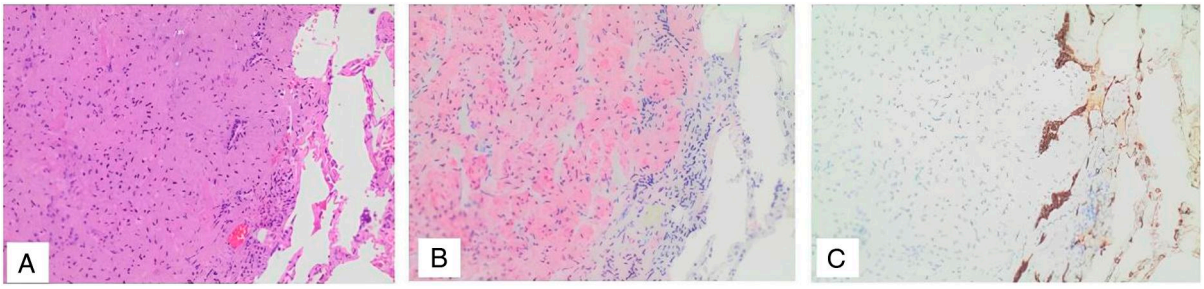

FIGURE 4. (A) Granular cell tumor characterized by epithelioid cells with abundant eosinophilic granular cytoplasm, central vesicular nucleus with occasionally prominent nucleolus, hematoxylin-eosin (100×); (B) S100 expression (100×); (C) CKAE1/AE3 negativity (100×)

is a well-established multiorgan cancer susceptibility gene, and alterations within its kinase domain may impair checkpoint control and contribute to tumorigenesis.[8] To our knowledge, *CHEK2* p.I200T has not been previously reported in granular cell tumors, and its role in GCT pathogenesis remains unexplored.

In this case, despite the presence of multiple variants of uncertain significance (VUS), the tumor displayed features of genomic stability, including absence of microsatellite instability (MSI), low tumor mutational burden (TMB <10 mut/Mb), and no alterations in homologous recombination repair (HRR) genes. Nonetheless, loss of heterozygosity (LOH) in *BRCA1* and *STK11*, as well as VUS in *ATM* and other cancer-related genes, were detected. Although none of these alterations were classified as pathogenic, they may represent a background of genomic instability or incidental passenger events. A *MET* variant with a VAF of 100% was also identified; however, its biological significance remains unclear and may reflect a germline SNP or a technical artifact. A comprehensive list of detected variants is outlined in Table 1.

DISCUSSION

Malignant GCTs remain poorly understood, and the gray zone, characterized by lesions with metastatic potential or local aggressiveness, still needs to be better investigated and characterized. Moreover, a standardized nomenclature is still lacking.

In 1998, Fanburg-Smith et al.[9] proposed 6 histologic criteria for selection of atypical or malignant cases in their study of 73 cases of GCT. These criteria are: increased

TABLE 1. Comprehensive List of Somatic Variants Detected by Targeted NGS Analysis in Both the Primary Vulvar Lesion and the Pulmonary Metastasis

Gene	Variant type	VAF (%)	Transcript ID	cDNA change	Protein change	Classification
CHEK2	SNV	48.35	NM_0010057.35.2	c.599T > C	p.(I200T)	Likely pathogenic
STK11	LOH	1.00	—	—	—	—
ATM	SNV	46.28	NM_000051.4	c.2932T > C	p.(S978P)	VUS
BARD1	SNV	48.26	NM_000465.4	c.1571A > G	p.(N524S)	VUS
CSF1R	SNV	44.48	NM_005211.4	c.317G > A	p.(R106Q)	VUS
HIST3H3	SNV	46.29	NM_003493.3	c.161G > A	p.(R54H)	VUS
IRS2	SNV	51.11	NM_003749.3	c.2635_2645delinsAGCTTCTTGGC	p.(G879_G882delinsSFLA)	VUS
KNSTRN	SNV	50.77	NM_033286.4	c.137G > A	p.(G46D)	VUS
MAP3K4	SNV	13.82	NM_005922.4	c.3596_3599delinsTTGC	p.(A1199_V1200delinsVA)	VUS
MET	SNV	100.00	NM_000245.4	c.3259+845G > T	—	VUS
MGA	SNV	45.86	NM_001164273.2	c.5314C > T	p.(P1772S)	VUS
PMS2	SNV	46.88	NM_000535.7	c.1004A > G	p.(N335S)	VUS
RASA1	SNV	53.99	NM_002890.3	c.454A > G	p.(T152A)	VUS
RICTOR	SNV	46.60	NM_152756.5	c.1364T > C	p.(M455T)	VUS
ROS1	SNV	46.81	NM_002944.3	c.1667C > A	p.(P556H)	VUS
RUNX1 T1	SNV	50.44	NM_001198679.2	c.1188A > T	p.(Q396H)	VUS
SERPINB4	SNV	30.32	NM_002974.4	c.1090_1091inv	p.(C364H)	VUS
SPEN	SNV	47.78	NM_015001.3	c.676C > T	p.(R226W)	VUS
TERT	SNV	100.00	NM_198253.3	c.-79-889T > C	—	VUS
TERT	SNV	100.00	NM_198253.3	c.-79-1303T > C	—	VUS
TERT	SNV	100.00	NM_198253.3	c.-79-2075A > G	—	VUS
TYRO3	SNV	23.30	NM_006293.4	c.1382+2T > C	—	VUS

The table includes gene name, mutation category (SNV or LOH), variant allele frequency (VAF) or copy number, corresponding cDNA and protein-level changes, and predicted biological impact. Mutations classified as variants of uncertain significance (VUS) are listed alongside likely pathogenic alterations. *CHEK2* p.I200T mutation was the only variant annotated as likely pathogenic and was shared across both lesions, suggesting a potential germline origin.

nuclear-to-cytoplasmic ratio; nuclear pleomorphism; necrosis; spindling of tumor cells; vesicular nuclei with prominent nucleoli; more than 2 mitoses per 10 high-power fields (HPF, 400× magnification). Based on these criteria, they adopted a three-tier classification dividing them into benign (none of the criteria or focal pleomorphism), atypical (1–2 criteria), and malignant (3–6 criteria).[9] However, in the Fanburg-Smith and colleagues report, except for the increased local recurrence rate and increase in the expression of Ki-67 (>10%) and p53, atypical and benign tumors did not metastasize or end in patient death.[9] However, the Fanburg-Smith criterion of "increased p53" reflects older, nonspecific interpretations of p53 immunoreactivity and should be considered cautiously in light of current, more refined approaches to p53 IHC interpretation. In 2004, Wang et al.[10] published a series of 10 cases of MGCTs reproducing Fanburg-Smith criteria, but recommended using a count of 5 mitoses per 50 HPF instead of 2 mitoses/10 (400× fields).

In 2007, Kapur et al.[11], in their study of 25 cases, considered metastasis as the sole criterion for malignancy. Using Fanburg-Smith criteria, they only classified their tumors into benign or atypical, even though some cases possessed more than 2 histologic criteria for malignancy.[11]

They reproduced the significant increase in Ki-67 in their atypical cases and also demonstrated an even greater increase in the phosphorylated Histone H3 immunostain in those cases. In contrast, Le et al.[12], in their study of 30 cases, reported no difference in Ki-67 expression between benign and atypical cases. Later, Torrijos-Aguilar et al.[13] published a series of 34 cases (1 malignant, 2 atypical, and 31 benign) without any metastases or recurrences. Nasser and colleagues noticed that necrosis and mitoses were highly segregated from malignant cases. These 2 histologic features are reliable indicators of malignancy across most tumor types, with high interobserver reproducibility.[14] Clinical features such as a size >5 cm, multicentricity, rapid growth, and recurrent disease may further increase the likelihood of malignant biological behavior.

On the other hand, some authors have emphasized that even in the absence of overt histologic features of malignancy in the vulvar primary, granular cell tumors may still lead to significant morbidity and even mortality due to their potential for multicentric growth and multiorgan involvement.[15,16]

From a pathologic perspective, the diagnosis of granular cell tumor can be challenging due to its potential morphologic overlap with a wide spectrum of entities. These include reactive histiocytic lesions (such as mycobacterial pseudotumor/histoid leprosy, malakoplakia, Rosai–Dorfman disease, granular cell reaction, and cellular spindled histiocytic pseudotumor), soft tissue neoplasms (rhabdomyoma, hibernoma, benign fibrous histiocytoma, leiomyoma/leiomyosarcoma, angiosarcoma, and undifferentiated pleomorphic sarcoma/atypical fibroxanthoma), as well as malignant melanoma.[12–14] An appropriate immunohistochemical panel can therefore be crucial in establishing the diagnosis: GCTs typically show positivity for S100, SOX10, CD68, inhibin A, NSE, CD56, EMA, calretinin, and TFE3, with negative staining for CD31, CD34, alpha–smooth muscle actin, desmin, GFAP, synaptophysin, chromogranin, HMB45, Melan-A, ER, and PR.[12–14]

Although the genetic drivers of GCTs are not fully understood, whole-exome and targeted sequencing studies have identified mutually exclusive, clonal, inactivating somatic mutations in the endosomal pH regulators ATP6AP1 or ATP6AP2 in ~72% of cases. These alterations likely contribute to the formation of the characteristic intracytoplasmic granules that define the tumor's morphology.[17]

Other authors reported subclonal mutation of PIK3CA p.H1047R with a low mutant allele frequency of 7%, which may represent an evolving subclone and might confer a more aggressive behavior.[18] However, our NGS panel did not include ATP6AP1 and ATP6AP2 and did not reveal PIK3CA alterations.

The present case study highlights a distinctive feature that underscores its uniqueness compared with previously reported cases: its reliance on the presence of metastases as the sole criterion for malignity. This, combined with the rarity of the lesion, complicates the understanding of its biological behavior. Interestingly, despite the absence of overt histologic features of malignancy, the metastatic behavior of the tumor and the presence of a potentially pathogenic *CHEK2* mutation raise questions about additional molecular determinants of aggressiveness beyond conventional histology. To our knowledge, no *CHEK2* mutations other than the p.I200T variant reported here have been previously documented in granular cell tumors at any site. In this context, the *CHEK2* variant identified in our patient may represent a cooperating molecular event, potentially facilitating tumor progression or metastatic potential, although additional studies are needed to clarify its biologic relevance in granular cell tumor pathogenesis. In addition, the past medical history of nephroblastoma in childhood is noteworthy; however, no established association between *CHEK2* variants and nephroblastoma has been described, and the absence of archival tissue from the prior tumor prevented us from determining whether the *CHEK2* variant identified in the current neoplasm was germline or shared by the earlier malignancy.

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