CASE REPORT

Atypical Multifocal Granular Cell Tumor with FLT3 Y842C Somatic Mutation: A case report and a review of the literature

Tumeur atypique multifocale a cellules granuleuses avec altération somatique FLT3 Y842C: Un rapport de cas et revue de la littérature

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Abstract

Introduction: Granular cell tumors (GCT) are predominantly benign neoplasms composed by cells with abundant eosinophilic granular cytoplasm. Although the majority of GCTs exhibit a benign clinical course, a minority display cytological atypia and may exhibit aggressive, cancer-like behavior. Definitive evidence of malignancy in GCTs is reliably established only through the presence of metastasis. Additionally, a subset of GCTs demonstrates a high rate of recurrence, underscoring the need for better prognostic markers. Therefore, it is crucial to identify molecular markers associated with aggressive behavior in GCTs. Molecular analysis may be particularly beneficial in cases exhibiting cytological atypia to inform clinical outcome prognostication and guide therapeutic strategies.

Observation: In this case report, a 45-year-old female with multiple gastrointestinal GCTs is presented. The patient did not have any genetic syndromes commonly associated with GCT, such as neurofibromatosis type 1, Noonan syndrome or LEOPARD syndrome. The tumors not only demonstrated nuclear atypia, but also harbored a unique FLT3 Y842C somatic alteration identified by next-generation sequencing. The patient remains asymptomatic and under endoscopic surveillance two years after diagnosis and complete resection of the neoplasms.

Conclusion: We presented an exceedingly rare case of multifocal atypical GCT in an adult without any previously known genetic syndrome. A tumoral FLT3 Y842C point mutation not previously reported in GCT was discovered. Although the precise significance of this finding is uncertain, FLT3 Y842C has been cataloged as likely pathogenic in ClinVar. This report underscores the potential predictive utility of next-generation sequencing in the characterization and management of rare neoplasms.

Key words: Case Report, Endoscopy, Immunohistochemistry, Next-Generation Sequencing

Résumé

Introduction: Les tumeurs à cellules granuleuses (TCG) sont des tumeurs principalement bénignes ca- ractérisées par des cellules avec un cytoplasme granulaire éosinophile abondant. Bien que la majorité des TCG aient une évolution clinique bénigne, une minorité présente une atypie cytologique et un compor- tement agressif semblable à celui du cancer. La preuve définitive de malignité dans les TCG est établie uniquement par la présence de métastases. De plus, un sous-ensemble de TCG montre un taux élevé de récidive, soulignant la nécessité de marqueurs pronostiques fiables. Par conséquent, il est crucial d'iden- tifier des marqueurs moléculaires associés à un comportement agressif dans les TCG. L'analyse molécu- laire peut être particulièrement bénéfique dans les cas présentant une atypie cytologique pour mieux prédire l'évolution clinique et guider les stratégies thérapeutiques.

Observation: Nous rapportons le cas d'une femme de 45 ans présentant plusieurs TCG gastro-intesti- nales. La patiente ne présentait aucun syndrome génétique couramment associé aux TCG, tels que la neurofibromatose de type 1, le syndrome de Noonan ou le syndrome LEOPARD. Les tumeurs montraient non seulement une atypie nucléaire, mais comportaient également une altération somatique unique FLT3 Y842C identifiée par séquençage de nouvelle génération. Deux ans après le diagnostic et la résection complète des tumeurs, la patiente reste asymptomatique et sous surveillance endoscopique.

Conclusion: Nous présentons un cas extrêmement rare de TCG atypiques multifocales chez un adulte sans aucun syndrome génétique connu auparavant, présentant une mutation ponctuelle oncogénique FLT3 Y842C non rapportée auparavant dans les TCG. Bien que la signification précise de cette décou- verte soit incertaine, FLT3 Y842C a été cataloguée comme probablement pathogène dans ClinVar. Ce rapport souligne l'utilité prédictive potentielle du séquençage de nouvelle génération dans la caractérisa- tion et la gestion des tumeurs rares.

Mots cles: Endoscopie, Immunohistochimie, Rapport de cas, Séquençage de nouvelle génération

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Introduction

Granular cell tumors (GCT) are rare and predominantly benign neoplasms characterized by cells with abundant eosinophilic granular cytoplasm that in some cases can display cytological atypia and exhibit aggressive, cancer-like behavior [1]. Although the histopathology of regular GCT without cytologic atypia has been well defined [2], only nine cases [3-10] of atypical granular cell tumor (AGCT) were identified in PubMed since 2014. Interestingly, these studies have not elucidated the significance of cytologic atypia in GCT, which may be in part due to the lack of molecular analysis and the rarity of the phenomenon. AGCT represents less than 1% of GCT [11], and comprise 0.5% of soft tissue tumors [12].

The exact criteria for atypia in GCT are still lacking, and nuclear features, such as pleomorphism, hyperchromasia, or the presence of nucleoli have been described. In addition, high nuclear/cytoplasmic ratios and necrosis are considered [13]. AGCT can occur at any age or site and are more common in adult females [1]. Till the end of August 2024, definitive evidence of malignancy in GCT is established only through the presence of metastasis, underscoring the need for reliable prognostic and molecular markers associated with aggressive behavior [1]. Because the natural history of GCT, including the rate of progression from benign to atypical or malignant forms, is not well understood, exact management and prognostication are still evolving. Complete resection with clear margins is the standard treatment and a significant yet imprecise rate of recurrence has been described [13]. Therefore, there is a pressing need to enhance our understanding of the molecular pathology of AGCT, with the goal of developing more effective therapies, which may include targeted drugs.

Our case report aimed to shed light on a novel mutation identified through next-genera- tion sequencing in a patient who developed multifocal AGCT.

Case report

A 45-year-old black female with no significant previous medical history was found to have iron-deficiency anemia on a routine wellness visit and a gastrointestinal endoscopy was performed, which revealed several subepithelial lesions (Figure 1). The patient consented to publish these results.

Specifically, three gastric nodules (measuring 0.5, 0.9, and 1.1 cm in the largest dimension), two colonic “polyps” (measuring 1 and 1.5 cm), and one rectal nodule measured to 0.5 cm were found. All the lesions were inconsistent with lipoma due to a negative endoscopic pillow sign, and were biopsied and submitted for pathologic evaluation. Morphologic analysis of all lesions identified well-circumscribed submucosal GCTs with moderate nuclear atypia, including pleomorphism, enlargement, and hyperchromasia on hematoxylin and eosin (H&E) staining (Figure 2).

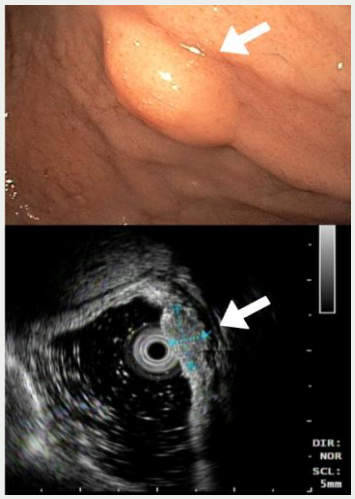

Figure 1. Representative pillow sign-negative subepithelial lesion in the stomach

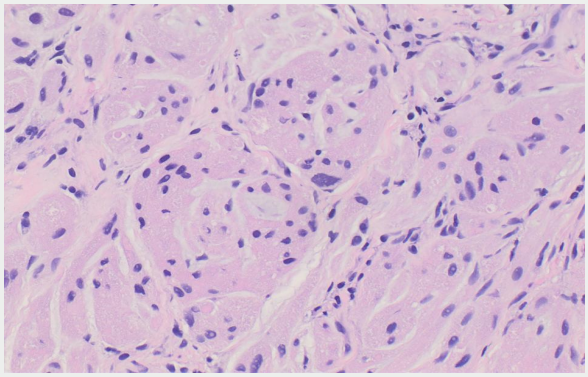

Figure 2. Histopathology micrographs of a gastric lesion at 400x. H&E stain

Immunohistochemical stains were positive for S100 and CD68 but negative for CD34, CD31, CD117, desmin, epithelial membrane antigen (EMA), P53 and smooth muscle actin (SMA) (Figure 3).

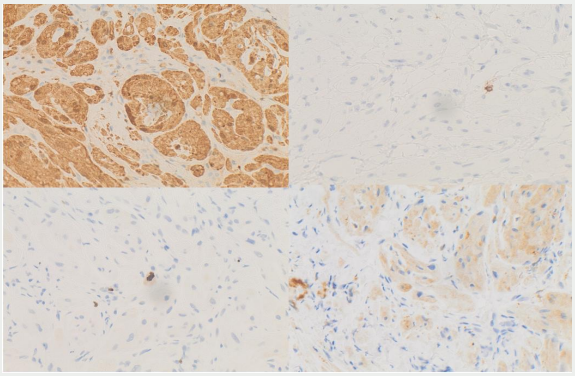

Figure 3. Immunohistochemistry micrographs of a representative lesion. All at 400x. Upper left corner: S100; upper right corner: CD117; lower left corner: Ki67; lower right corner: CD68.

Additionally, the tumors exhibited a low proliferation rate on Ki-67 immunostaining. Because of the presence of cytologic atypia and the also uncommon multifocal presentation, next- generation sequencing (Ion Torrent OncomineFocus Assay, Thermo Fisher Scientific) was performed identifying a somatic point mutation Y842C in the FLT3 (Fms-like tyrosine kinase 3) gene. Genetic consultation and detailed physical examination ruled

out increased genetic risk or the presence of syndromic dysmorphism. Follow up repeat colonoscopy three months after the diagnosis of multiple GCTs (MGCT) revealed a 0.3 cm minimally elevated, polyp in the ascending colon, which was completely removed with cold snare technique. This polyp was diagnosed as a tubular adenoma (data not shown) by routing histopathologic examination. In addition, a follow up upper endoscopy was performed three months after the more recent colonoscopy, and two areas of scarring were seen in the gastric body at the site of previous biopsy. Due to the observed cytologic atypia and genetic alteration in the prior specimen, banding and resection were done to rule out possible residual neoplasm. Reassuringly, histopathologic examination of this new biopsy material (including immunohistochemistry for S100) failed to demonstrate recurrent/residual GCTs (data not shown). The patient remains asymptomatic and under periodic endoscopic surveillance, two years after diagnosis.

Discussion

Our report highlighted a possible association between an atypical presentation of MGCT and a FLT3 somatic alteration. To the best of the authors' knowledge only nine cases of AGCT were published in PubMed since 2014 (Table 1).

Table 1. Atypical granular cell tumor cases reported in PubMed from 2014 to 2024

Case	Age (years)	Ethnicity	Sex	Location	Atypical features on H&E	Multifocal	Necrosis	IHC	Molecular Analysis	Treatment	Recurrence/ Metastases	References
1	50	Not reported	M	Bladder	Spindle cells, mild nuclear atypia , few mitoses	No	No	S100(+), Vimentin(+), Ki-67(1-2%)	Not done	Excision	No (3 month follow-up)	Movahed et al [3]
2	32	Not reported	F	Skin (abdomen)	Nuclear pleomorphism, mitotic rate of 1/10HPF	No	No	S100(+), MelanA(-), HMB45(-), tyrosinase(-)	ATP6AP2 pY326*, premature stop codon	Re-excision	Unknown	Warren et al [4]
3	57	Not reported	M	Skin (back)	Spindle cells, mitotic rate of 1/10HPF	No	No	S100(+), SOX10(+), PGP9.5(+), MelanA(-), HMB45(-), tyrosinase(-)	ATP6AP1 pN406fs, loss of function	Re-excision	Unknown	Warren et al [4]
4	59	Not reported	F	Median nerve (right forearm)	Large nuclei with prominent nucleoli, high N:C ratio, pleomorphism, mitotic rate of 2/10 HPF	No	Yes	S100(+), CD68(+), SMA (+), SOX-10(+), Calretinin(+), TFE3(+), Ki-67(10%)	Not done	Excision	No (2 month follow-up)	Liu et al [5]
5	62	Chinese	F	Bladder	Pleomorphism, vacuolar and obvious nuclei, increased N:C ratio, mitotic rate of 0-1/10HPF	No	No	S100(+), NSE (+), Ki-67(weak/5%), CD68(weak), Pancytokeratin(-)	Not done	Excision	No (6 month follow-up)	Wei et al [6]
6	54	Caucasian	F	Bladder	Spindle cells and pleomorhphism	No	No	S100(+), NSE(+), Ki-67(5%), Pancytokeratin(-), CD68(-)	Not done	Excision	No (36 month follow-up)	Tuffano et al [7]
7	43	Caucasian	M	Skin (right arm within a tattoo)	Ulceration	No	No	S100(+), CD68 (+), Cytokeratin 8/18 (-), MelanA(-)	Not done	Excision	Unknown	Brunsgaard et al [8]
8	69	Not reported	F	Subcutis and muscle (neck)	Moderate nuclear atypia, pleomorphism, spindle cells, desmoplastic stroma	No	Not reported	S100(+), CD68 (+), vimentin(+), NSE(+), Ki-67(<1%), p53(50%)	Not done	Excision	No (11 month follow-up)	Nakamura et al [9]
9	16	Not reported	F	Intraosseous (maxilla)	Spindle cells, large vesicular or hyperchromatic nuclei, prominent nucleoli, pleomorphism, mitotic rate of 2/10HPF	No	Not reported	S100(+), CD68 (+, intracytoplasmic granules), CD56(+), Ki-67(10%), p53(+), cytokeratin(-), desmin(-), SMA (-), c-kit(-)	Not done	Excision	No (4 month follow-up)	Oh et al [10]

F, female; **H&E**, hematoxylin and eosin; **HMB45**, human melanoma black; **HPF**, high power field; **M**, male; **MelanA**, melanoma antigen; **N:C**, nuclear to cytoplasmic; **NSE**, neuron-specific enolase. **PGP 9.5**, protein gene product; **SMA**, smooth muscle actin; **TFE3**, transcription factor binding to IGHM Enhancer 3; **Yr**, years.

GCT, also known as Abrikossoff tumor, is a rare soft tissue neoplasm of neuroectodermal origin, characterized by abundant eosinophilic cytoplasm with distinctive intracytoplasmic granules, believed to represent lysosomes [1]. GCTs are usually benign and can present on any soft tissue site (including internal organs) with higher prevalence in the head and neck of middle-age adult black women [1]. Only approximately < 2% of GCTs are malignant, and distinguishing them from benign or atypical forms is still debated in part due to histologic variation and the rarity of the entity [13]. Malignancy can be favored in the presence of necrosis, enlarged nuclei or high mitotic rate, however, most cases do not display such features and metastasis remains the only firm diagnostic criteria of cancer [1,13]. Therefore, the molecular pathology of GCT remains and important area of investigation with the hope of identifying alterations that can reliably predict aggressive behavior and/or offer druggable targets. Interestingly, the majority of GCTs are solitary lesions, but MGCT have been described in 30% of cases, including 8% with familial association, more commonly in patients with neurofibromatosis type 1, Noonan syndrome or LEOPARD syndrome (LS) [14,15]. Various genetic alterations (not covered in our NGS panel, namely in ATP6AP1, ATP6AP2, GFRA2, BRD7, PTPN11 and PTEN) have been discovered in GCT [14,16,17]. Silencing of endosomal pH regulator genes (ATP6AP1 or ATP6AP2) in vitro leads to intracellular changes recapitulating GCT and induces oncogenic properties [16]. The PTPN11 T468M mutation was reported in a patient with LS and MGCT, linking deregulation of the Ras/mitogen-activated protein kinase (MAPK) signaling pathway to this neoplasm [14,15]. Herein, we uncovered a novel FLT3 alteration associated with a non syndromic case of MGCT.

FLT3 encodes a transmembrane tyrosine kinase class III receptor that upon cytokine binding signals survival, proliferation and differentiation in various cells, including myeloid and lymphoid lineages [18]. FLT3 is a well-stablished proto-oncogene most commonly associated with acute leukemias (AML) and other hematologic malignancies, but also described in association with colorectal carcinoma, lung carcinoma, melanoma and metastatic breast carcinoma [18,19]. Even though its exact pathogenic mechanism is still being elucidated, constitutive activation of FLT3 after alterations in the juxtamembrane domain or the intracellular tyrosine kinase domain (TKD) leads to deregulation of downstream signaling pathways, such as STAT5, PI3K/AKT, and MAPK. Of interest, alteration of PTPN11 in GCT also affects MAPK [16], which may be an example of convergent clonal evolution. However, alterations of FLT3 have not been reported in GCT and are present in only 1.27% of sarcomas in the AACR Project GENIE database [20].

Intriguingly, the identified Y842C lies in the highly conserved TKD2 activation loop of FLT3 [10,11], suggesting a likely pathogenic role in GCT. Notably, several Food and Drug administration (FDA) approved FLT3 inhibitors are currently in use in AML, which opens the opportunity to explore their potential therapeutic role in aggressive GCT (recurrent after surgery or metastatic).

Limitations

Our case has certain limitations worth discussing. Because this is the first report of atypical MCGT with FLT3 mutation, generalizability of its significance is uncertain, and further research either on clinical cases or in ex-vivo functional transfection models (both beyond the scope of this case report), is necessary to clarify the biological impact. Similarly, epidemiologic analysis including survival, or environmental/lifestyle factors associated with AGCT cannot be analyzed in our report, but the data may be pertinent in the future.

Conclusion

We reported a case of an adult female with sporadic MGCT characterized by cellular atypia and a previously unreported somatic FLT3 Y842C alteration. These findings highlight the opportunity for further research on the FLT3 Y842C mutation in GCTs to advance our understanding of the genetic and molecular pathogenesis, and to explore the therapeutic potential of available inhibitors in the future.

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