A Tumor of Composite Cervical Adenocarcinoma with MUCIN Gene Mutation： A Case Report

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Research

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Abstract

Background: There are reports about the coexistence of two kinds of tumors in the same patient,which is believed that this phenomenon is caused by the dedifferentiation between the two tumors.In this paper, we report an human papillomavirus (HPV) negative cervical adenocarcinoma in a patient composed of two adenocarcinoma components,which is first reported.Histologically, both minimal deviation adenocarcinoma (MDA) and poorly differentiated gastric type adenocarcinoma (GTA) components, as well as their transitional area, were observed.

Methods: This case of cervical cancer was screened by gene sequencing. For detection of specific somatic mutations in MDA and GTA, we filtered out mutations in malignant cervical cancer blood sample and 7 common cervical carcinoma. Then the genes were screened and identified based on the enrichment analysis of GO and KEGG and related literature reports.

Results: We found 13 specific somatic gene mutations in total. Among these genes, only Mucin gene was transformed from gene level to protein level, and was positive in both MDA and GTA components of the patient by immunohistochemistry.Both components had genes mutation of MUC4 and MUC17,the component in MDA had gene mutation of MUC3A,and we found that MUC3A and MUC17 were on the same chromosome. Moreover,MUC3A and MUC4 genes were found to be fused in FusionGDB database.

Conclusion: According to the reports of MUC3A,MUC4 and MUC17 genes mutation in cervical adenocarcinoma and gene fusions in tumorigenesis, we speculate that the occurrence of the transformation of pathological type from MDA to GTA in this case of cervical cancer is related to the mechanism of MUC3A and MUC4 gene fusion.We would advice, for HPV negative or atypical cervical lesions, immunohistochemistry of MUCIN genes staining and gene sequencing should be considered, which may find unusual cancer types and change the prognosis of patients.

Background

Minimal deviation adenocarcinoma (MDA) of cervical is not associated with persistent HPV infection, and it is difficult to be found in cytological and biopsy specimens because of its deep location, endogenous growth pattern and slight cytological atypia[1,2]. It represents 1-3% of cervical adenocarcinomas and is characterised morphologically by extremely well differentiated glands with little in the way of nuclear atypia[1,2].Recently, another variant of cervical adenocarcinoma has been described which is thought to exhibit gastric differentiation[4]. This has been termed ‘gastric type’ adenocarcinoma (GTA) and, in contrast to MDA, is characterised by obvious malignant cytological features[4]. Mcclugage et al.[5] found that there was a similar genetic variation between MDA and GTA, indicating that there was a specific relationship between the two kinds of tumors. They believed that GTA was dedifferentiated from MDA[6].As far as we know, at present, only two literatures have described the diagnosis of GTA accompanied by MDA, but they all lack the poorly differentiated gastric adenocarcinoma seen in this case[7,8]. In this case, the MDA and GTA components with different differentiation appeared simultaneously in cervical tumor, and the two components had similar immunophenotypes, which was consistent with the diagnosis of different differentiation of the same tumor. The continuity between the MDA and GTA components favors the hypothesis that GTA arises from the dedifferentiation of MDA, however, the mechanism of this dedifferentiation remains unclear. In this study, we did gene sequencing of the tumor and blood of the patient. According to the existing reports, we found some related gene mutations, which may be related to the tumor dedifferentiation mechanism of this patient.

A Case Report

A 54-year-old woman presented to our hospital with abnormal vaginal bleeding for one month. Physical examination revealed normal external genitalia and a fragile neoplasm which is 1cm in diameter without obvious active bleeding in the cervix, and the origin of the neoplasm was unclear. Transvaginal sonography revealed uneven hypoechoic with a size of 6.3×6.5×4.6 cm in the lower segment of the uterus,uneven echo of endometrium with a thickness of 0.25cm.The cytological tests reported the presence of atypical glandular cells of undetermined significance(AGUS), which was in favor of the diagnosis of adenocarcinoma of the endocervix. Human papillomavirus E6/E7 mRNA was negative. However, despite undergoing endometrial curetting and cervical biopsy, she was diagnosed with only chronic cervical inflammation and polyps, and not with cervical or endometrial malignancy. All laboratory data including serum CA-125, SCC-Ag, CEA, AFP and CA19-9 were within normal ranges Radiological examination showed no tumour outside the cervix. Subsequently, the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. According to pathological section, she underwent radical parametrectomy with removal of a vaginal cuff and pelvic lymph node dissection. The patient died after a course of radiotherapy

Materials And Methods

1.Immunohistochemistry

For the immunohistochemical analysis of primary antibodies against gastric gland mucin(MUC4,ab150381;Abcam,USA; and MUC3A,ab199260;Abcam,USA), 4-μm serial tissue sections from the formalin-fixed, paraffin-embedded tissues were used. The samples were deparaffinized in xylene and rehydrated through a graded series of ethanol washes. After the endogenous peroxidase was inhibited and the antigen was retrieved (microwave irradiation in 0.01 M citrate buffer at pH 6.0), the sections were incubated with primary antibody at 4°Covernight and then with horseradish peroxidase (HRP)-conjugated secondary antibodies (DakoCytomation, Denmark). After washing, tissues were stained for 5 min with 3,30-diaminobenzidine (DAB) chromogen and counterstained with hematoxylin (Zhongshan Golden Bridge,Inc), dehydrated and mounted on cover slips.

2.DNA extraction and whole genome sequencing

Genomic DNAs were extracted from peripheral whole blood and Formalin-fixed paraffin-embedded samples (including MDA and GTA) of malignant cervical cancer and 7 FFPE samples (including 3 adenocarcinoma and 4 squamous carcinoma) of common cervical cancer by using Qiagen Blood DNA mini Kit and QIAamp DNA FFPE Tissue Kit (Qiagen, Germany) according to the manufacturer's recommendations. Briefly, genomic DNAs extracted from 9 tumors and 1 matched peripheral whole blood were purified and DNA from peripheral whole blood fragmented randomly. 5-10μg genomic DNA was used for library generation and standard paired-end adaptors were ligated according to the manufacturer's (Illumina) protocol. Each of libraries were subjected to WGS on an Illumina HiSeq 2000. Target depth (30× for tumors and peripheral whole blood samples) was achieved in all samples.

3.Somatic variant identification

Through the investigation of no history of malignant tumor in the three generatios of relatives of this patient with highly malignant cervical cancer, it is considered that the occurrence and development of this cervical cancer was unlikely to be due to genetic factors and probably due to somatic mutation. For detection of somatic point mutations, sequencing reads from a Illumina HiSeq 2000 were aligned to the human reference genome (UCSC Genome Browser hg19) with the Burrows-Wheeler Aligner. After duplicate reads were removed with SAMtools, an in-house pipeline was used to call somatic mutations. The indel-calling step was performed by the Genome Analysis Toolkit SomaticIndel Detector with default parameters. Severe somatic variants including stopgain, frameshift, insertion/deletions (indels) and nonsynonymous SNVs were identified in minimal deviation adenocarcinoma and gastric type adenocarcinoma but absent in the adjacent bloods.

4.Data analysis

For detection of specific somatic mutations in MDA and GTA, we filtered out mutations in malignant cervical cancer blood sample and 7 common cervical carcinoma and the GnomAD_ALL_Value<0.01 was selected(Figure 1). The mutations were annotated to public databases by Annovar. GO analysis and KEGG enrichment analysis were carried out on the mutations obtained. Databases such as OMIM (http://www.omim.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), Human Gene Mutation Database (http://www.hgmd.org) and SwissVar (http://www.bioinfo.org/wiki/index.php/SwissVar) were used to determine mutation harmfulness and pathogenicity where appropriate.A total of 10 Signaling pathway associated with cancer progression including RTK/RAS pathway, Nrf2 pathway, PI3K pathway, Wnt pathway, Myc pathway, P53 pathway, TGF-β pathway, Hippo pathway, Cell cycle pathway, Notch pathway were selected for exploring specific somatic mutations associated with malignant cervical cancer.

Results

1.Histological findings

Histological examination revealed that the tumor was composed of two adenocarcinoma components: 1) MDA: There was effacement of the normal endocervical glandular architecture by a proliferation of well differentiated glands with infiltrative growth, in keeping with MDA (Figure2A and 2B); The nuclei are basally located and the cytoplasm is abundant and clear. Fibrous connective tissue hyperplasia and inflammatory cell infiltration were found around the gland, two types of cells with or without heteromorphism in glands were found in this area. 2) GTA: GTA component consisting of undifferentiated mucinous glands with marked nuclear atypia and lots of mitotic figures located between the stroma of the cervical canal and the myometrium of the uterine, where tumor cells extended diffusely, without obvious adenoid or nest-like structure and infiltrated into the deep part of the cervical stroma and myometrium.(Figure 2C). Transitional area between the MDA and GTA components is detected(Figure 2D).Tumor thrombi were found in the vessels as well. There was bilateral uterine parauterine tissues and two pelvic lymph nodes infiltration for poorly differentiated component. No pathological abnormality was seen in fallopian tube/ ovary /cervical mucosa or endometrium.

Immunohistochemically, MDA cells were negative with P16, P40, ER and PR,were positive with MUC4, MUC3A and broad-spectrum cytokeratin CKpan,were positive with CEA which in cavity margin; GTA cells was negative with P16, ER, CD10, Caldesmon, synaptophysin, chromaffin A and CKpan, were partially positive with MUC4, MUC3A,CEA and P40,were weak positive with PR. Ki-67 labeling index in the MDA component was 2% while that in the GTA component was more than 90%, indicating the striking difference in proliferation between the two components.Figure 3

2. Genomic analysis of MDA and GTA components

The tumor in this case was negative in HPV genotyping. For detection of specific somatic mutations in MDA and GTA, we filtered out mutations in malignant cervical cancer blood sample and 7 common cervical carcinoma, we obtained 6092 mutation sites involving 3102 genes in MDA and 4915 mutation sites involving 2876 genes in GTA. And we filtered out mutations which the GnomAD_ALL_Value≥0.01, we obtained 34 mutation sites involving 34 genes in MDA and 10 mutation sites involving 10 genes in GTA(Figure 1).Based on the enrichment analysis of GO and KEGG and related literature reports,specific somatic gene mutations including RASSF1, MUC4, DSPP, ATXN1, MUC17, DDHD1, and ABCC1 were found in the GTA samples.Specific somatic gene mutations including ADCY3, MUC3A, SPHKAP, MUC4, PCDH12, MUC17, FAM186A, and HRC were found in the MDA samples(Table 1) . MUC4 and MUC17 genes are present in both MDA and GTA tissues, MUC3A and MUC17 were on the same chromosome. It is reported recurrent fusion genes that signifificantly impact both progression and overall survival and may act as drivers of the disease[26]. MUC3A and MUC4 genes were found to be fused in FusionGDB database (https://ccsm.uth.edu/FusionGDB/index.html).(Table 2)

Table 1.

Specific somatic gene mutations of MDA and GTA components

	Gene	Location	Position	CDS	Exon/Intronic	MUT	AA_change	Het	mut_type
1) GTA	RASSF1	3p21.31	chr3:50378176:T:A	NM_170714.1	exon1	c.61A>T	p.K21X	.	stopgain
	MUC4	3q29	chr3:195510396:A:C	NM_018406.6	exon2	c.8055T>G	p.H2685Q	.	nonsynonymous SNV
	DSPP	4q22.1	chr4:88537036:C:A	NM_014208.3	exon5	c.3222C>A	p.D1074E	.	nonsynonymous SNV
	ATXN1	6p22.3	chr6:16327915:A:C	NM_000332.3	exon8	c.627T>G	p.H209Q	het	nonsynonymous SNV
	MUC17	7q22.1	chr7:100678173:C:G	NM_001040105.1	exon3	c.3476C>G	p.T1159S	het	nonsynonymous SNV
	DDHD1	14q22.1	chr14:53619480:T:C	NM_001160147.1	exon1	c.337A>G	p.S113G	het	nonsynonymous SNV
	ABCC1	16p13.11	chr16:16162019:T:A	NM_004996.3	exon13	c.1684T>A	p.L562M	.	nonsynonymous SNV
2) MDA	ADCY3	2p23.3	chr2:25141434:G:C	NM_004036.4	exon2	c.423C>G	p.Y141X	.	stopgain
	MUC3A	7q22.1	chr7:100550767:-:A	NM_005960.1	exon4	c.1348dup	p.S450Yfs*118	het	frameshift insertion
	SPHKAP	2q36.3	chr2:228883721:T:A	NM_001142644.1	exon7	c.1849A>T	p.K617X	.	stopgain
	MUC4	3q29	chr3:195508510:A:G	NM_018406.6	exon2	c.9941T>C	p.L3314P	het	nonsynonymous SNV
	PCDH12	5q31.3	chr5:141324955:C:G	NM_016580.3	exon4	c.3546G>C	p.R1182S	hom	nonsynonymous SNV
	MUC17	7q22.1	chr7:100677642:C:G	NM_001040105.1	exon3	c.2945C>G	p.T982R	het	nonsynonymous SNV
	FAM186A	12q13.12	chr12:50746999:A:T	NM_001145475.1	exon4	c.3616T>A	p.S1206T	het	nonsynonymous SNV
	HRC	19q13.33	chr19:49657889:T:A	NM_002152.2	exon1	c.606A>T	p.E202D	het	nonsynonymous SNV

Table 2.

MUC3 and MUC4 genes were found to be fused in FusionGDB database

FusionGID	FusionGene	Hgene	HGID	Tgene	TGID
22879	MUC3A IL32	MUC3A	4584	IL32	9235
22880	MUC3A MUC3A	MUC3A	4584	MUC3A	4584
22881	MUC3A SET	MUC3A	4584	MUC3A	6418
7348	CLDN4 MUC4	CLDN4	1364	MUC4	4585
19917	LMO7 MUC4	LMO7	4008	MUC4	4585
22882	MUC4 MAGEF1	MUC4	4585	MAGEF1	64110
22883	MUC4 MUC4	MUC4	4585	MUC4	4585
22884	MUC4 PCYT1A	MUC4	4585	PCYT1A	5130
22885	MUC4 TNK2	MUC4	4585	TNK2	10188
35950	SREBF2 MUC4	SREBF2	6721	MUC4	4585
41638	VPS72 MUC4	VPS72	6944	MUC4	4585
(https://ccsm.uth.edu/FusionGDB/index.html).					

Discussion

We report an human papillomavirus (HPV) negative cervical adenocarcinoma in a patient composed of two adenocarcinoma components.Histologically, both minimal deviation adenocarcinoma (MDA) and poorly differentiated gastric type adenocarcinoma (GTA) components, as well as their transitional area, were observed. MDA is an uncommon but well known variant of cervical adenocarcinoma characterised by highly differentiated malignant glands and bland cytology. MDA is thought to exhibit gastric or pyloric differentiation based on histochemical and immunohistochemical studies.[10-13] It is associated with aggressive behaviour and a poor prognosis[4]. Dedifferentiated carcinoma cells lack the ability to maintain cell–cell contact, and therefore diffusely infiltrate the stroma, resulting in increased invasion and metastasis. Despite the paucity of data on the role of HPV in the development of MDA and GTA, it is believed that these lesions are not aetiologically related to HPV infection,[16,17]unlike the majority of usual type cervical adenocarcinomas which contain high risk oncogenic HPV[17], which complicates an early diagnosis of these tumors, even when a HPV DNA test is used. In the case of MDA in particular, obscure cell atypia makes it difficult to differentiate from normal cells. The tumor in this case was negative in HPV genotyping. This case may provide further evidence for this hypothesis. Both components were also p16 negative, in keeping with an absence of HPV, diffuse p16 staining in the cervix being a useful surrogate marker of the presence of high risk HPV.

There are reports about the coexistence of two kinds of tumors in the same patient,which is believed that this phenomenon is caused by the dedifferentiation between the two tumors[7-8,22].This case of cervical cancer was screened by gene sequencing. 13 tumor related genes were obtained by enrichment analysis of GO and KEGG and related literature reports. Among these genes, only Mucin was transformed from gene level to protein level, and was positive in both MDA and GTA components of the patient by immunohistochemistry. It is considered that Mucin gene may play an important role of biological processes like embryonic development, protein folding, cell signalling, immune responses and malignancies[18] in the occurrence and development of this case of cervical cancer. There are reports that MUC3 and MUC4 are related to tumor dedifferentiation, but the specific mechanism is unclear. Park HU et al. found that a decrease in the expression of MUC3 and MUC4 was correlated with the degree of dedifferentiation of the tumor.The highest expression of MUC3 and MUC4 proteins was observed in well-differentiated infiltrating adenocarcinoma, and expression of both gradually decreased in parallel with the dedifferentiation of carcinoma. MUC4 peptides showed a gradual decrease according to the degree of dedifferentiation of cancer, indicating the differentiation-dependent expression of mucin genes.[20-21].Some studies have shown that gene fusion may occur in mutated genes located on the same chromosome, and gene fusion can be found in a variety of dedifferentiated cancers, which may be related to the evolution of dedifferentiation of cancer[23-25].It is reported recurrent fusion genes that signifificantly impact both progression and overall survival and may act as drivers of the disease[9].Through gene detection, both MDA and GTA components in this case had genes mutation of MUC4 and MUC17,the component in MDA had gene mutation of MUC3A,and we found that MUC3A and MUC17 were on the same chromosome.Moreover,MUC3A and MUC4 genes were found to be fused in FusionGDB database (Figure 3),we speculate that the occurrence of the transformation of pathological type from MDA to GTA in this case of cervical cancer is related to the mechanism of MUC3A and MUC4 gene fusion.

Conclusion

In summary, we report an unusual HPV negative cervical adenocarcinoma with two morphologically components:MDA and poorly differentiated GTA.The mutation of MUC3A, MUC4 may be responsible for dedifferentation of MDA. We would advice, for HPV negative or atypical cervical lesions, immunohistochemistry of MUCIN genes staining and gene sequencing should be considered, which may find unusual cancer types and change the prognosis of patients.

Abbreviations

HPV=human papillomavirus,TCT=Thin-preparation cytologic test, CEA= Carcinoembryonic antigen, AFP=alpha-fetoprotein,CA125= Cancer antigen 125, WGS =whole-genome shotgun, GO analysis=Gene Ontology analysis,MDA=minimal deviation adenocarcinoma, GTA=gastric type adenocarcinoma,ATXN1=Ataxin-1, ABCC1= ATP-binding cassette subfamily C member 1, ADCY3= adenylate cyclase 3,HRC =Histidine-rich calcium binding protein, DSPP=dentin sialophosphoprotein, AGUS=atypical glandular cells of undetermined significance

Declarations

Ethics approval and consent to participate

The patient signed informed consent, and the study was approved by Women's Hospital, Zhejiang University School of Medicine Ethics Committee (201810254).

Consent for publication

I would like to declare on behalf of my co-authors that the patient has provided informed consent for publication of the case.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: S.M. Lv

Analysis and interpretation of data: M.J. Guo;G.P. Li

Writing and revision of the manuscript: M.J. Guo

Review of the manuscript:X.X. Jiang

All authors read and approved the final manuscript.

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References

1. Ishii K, Katsuyama T, Ota H, Watanabe T, Matsuyama I, Tsuchiya S, et al. Cytologic and cytochemical features of adenoma malignum of the uterine cervix. Cancer Cytopathol 1999;87:245-53.
2. Zhu L, Yi X, Lin B, Gao A, Zhao W, Zhang Y, et al. A clinicopathological and immunohistochemical study of minimal deviation adenocarcinoma of the uterine cervix. Med Hypotheses 2013;80:643-8.
3. Kaminski PF, Norris HJ. Minimal deviation carcinoma (adenoma malignum) of the cervix. Int J Gynecol Pathol 1983;2:141-52.
4. Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M, Nishimura R. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. Am J Surg Pathol 2007;31:664-72.
5. McCluggage WG, Harley I, Houghton JP, Geyer FC, MacKay A, Reis-Filho JS. Composite cervical adenocarcinoma composed of adenoma malignum and gastric type adenocarcinoma (dedifferentiated adenoma malignum) in a patient with Peutz Jeghers syndrome. J Clin Pathol 2010;63:935-41.
6. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol 2006;25:52-8.
7. Peng WX, Kure S, Ishino K, Kurose K, Yoneyama K, Wada R, et al. P16-positive continuous minimal deviation adenocarcinoma and gastric type adenocarcinoma in a patient with Peutz-Jeghers syndrome. Int J Clin Exp Pathol 2015;8:5877-82.
8. McCluggage WG, Harley I, Houghton JP, Geyer FC, MacKay A, Reis-Filho JS. Composite cervical adenocarcinoma composed of adenoma malignum and gastric type adenocarcinoma (dedifferentiated adenoma malignum) in a patient with Peutz Jeghers syndrome. J Clin Pathol 2010;63:935-41.
9. Cleynen A,Szalat R,Kemal SM,Robiou DP,Buisson L,Boyle E, et al.Expressed fusion gene landscape and its impact in multiple myeloma. Nat Commun 2017;8:1893.
10. Gilks CB, Young RH, Aguirre P, DeLellis RA, Scully RE. Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol 1989;13:717-29.
11. McCluggage WG. Endocervical glandular lesions: controversial aspects and ancillary techniques. J Clin Pathol 2003;56:164-73.
12. Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathology 2002;41:185-207.
13. Young RH, Scully RE. Invasive adenocarcinoma and related tumors of the uterine cervix. Semin Diagn Pathol 1990;7:205-27.
14. Mikami Y, Kiyokawa T, Hata S, Fujiwara K, Moriya T, Sasano H,et al. Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and 'adenoma malignum'. Mod Pathol 2004;17:962-72.
15. Utsugi K, Hirai Y, Takeshima N, Akiyama F, Sakurai S, Hasumi K. Utility of the monoclonal antibody HIK1083 in the diagnosis of adenoma malignum of the uterine cervix. Gynecol Oncol 1999;75:345-8.
16. Xu JY, Hashi A, Kondo T, Yuminamochi T, Nara M, Hashi K, et al. Absence of human papillomavirus infection in minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia. Int J Gynecol Pathol 2005;24:296-302.

17. Houghton O, Jamison J, Wilson R, Carson J, McCluggage WG. p16 Immunoreactivity in unusual types of cervical adenocarcinoma does not reflect human papillomavirus infection. Histopathology 2010;57:342-50.
18. Rao CV, Janakiram NB, Mohammed A. Molecular Pathways: Mucins and Drug Delivery in Cancer. Clin Cancer Res 2017;23:1373-78.
19. Gao L, Liu J, Zhang B, Zhang H, Wang D, Zhang T, et al. Functional MUC4 suppress epithelial-mesenchymal transition in lung adenocarcinoma metastasis. Tumour Biol 2014;35:1335-41.
20. Park HU, Kim JW, Kim GE, Bae HI, Crawley SC, Yang SC,et al. Aberrant expression of MUC3 and MUC4 membrane-associated mucins and sialyl Le(x) antigen in pancreatic intraepithelial neoplasia. Pancreas 2003;26:48-54.
21. Fukui Y. Mechanisms behind signet ring cell carcinoma formation. Biochem Biophys Res Commun 2014;450:1231-3.
22. Kai K, Satake M, Tokunaga O. Gastric adenocarcinoma of fundic gland type with signet-ring cell carcinoma component: A case report and review of the literature. World J Gastroenterol 2018;24:2915-20.
23. Liu W, Tong H, Zhang C, Zhuang R, Guo H, Lv C, et al. Integrated genomic and transcriptomic analysis revealed mutation patterns of de-differentiated liposarcoma and leiomyosarcoma. BMC Cancer 2020;20:1035.
24. Wang L, Motoi T, Khanin R, Olshen A, Mertens F, Bridge J,et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. Genes Chromosomes Cancer 2012;51:127-39.
25. Tardio JC, Machado I, Alemany I, Lopez-Soto MV, Nieto MG, Llombart-Bosch A. Solitary Fibrous Tumor of the Vulva: Report of 2 Cases, Including a De Novo Dedifferentiated Solitary Fibrous Tumor Diagnosed After Molecular Demonstration of NAB2-STAT6 Gene Fusion. Int J Gynecol Pathol 2018;37:547-53.

Figures

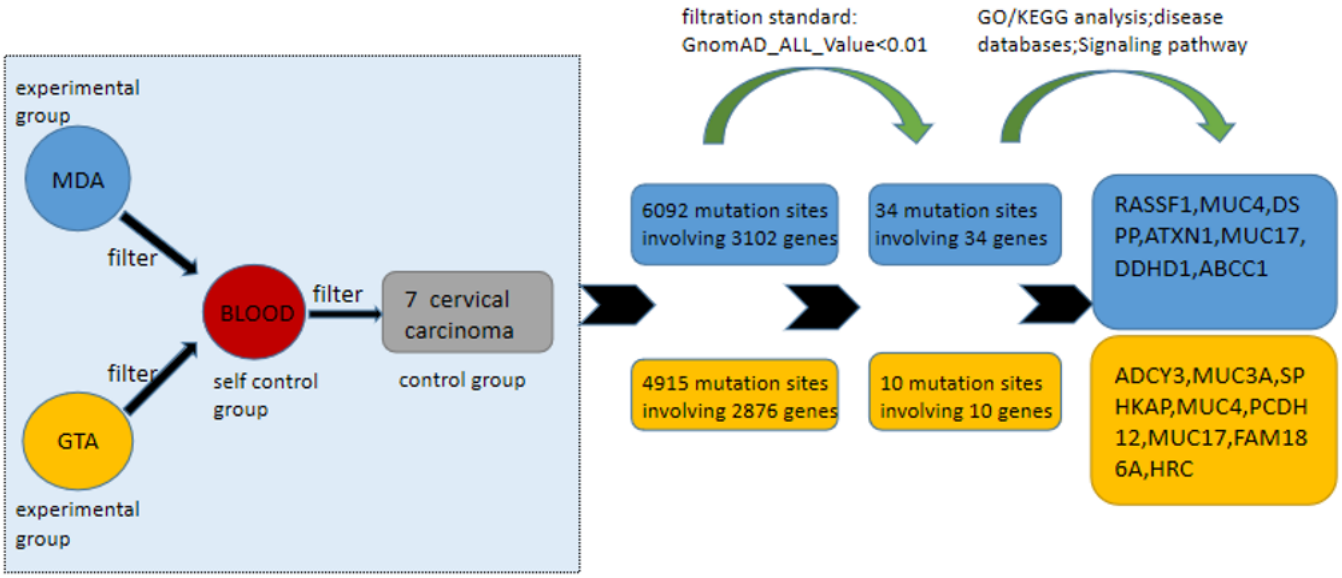

Figure 1

Workfow for the screening of the specific somatic gene mutations of MDA and GTA components

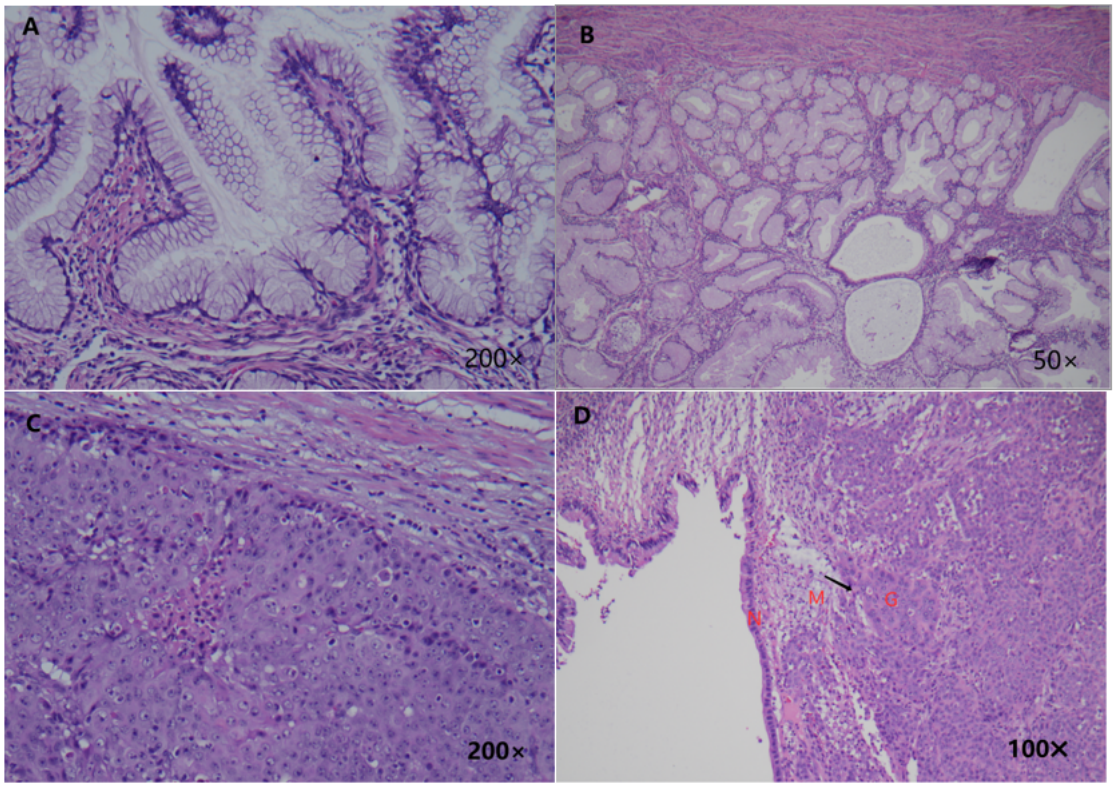

Figure 2

Histological findings HE. (A) MDA: The glands are lined by single-layer columnar cells without prominent atypia. The nuclei are basally located and the cytoplasm is abundant and clear.(B)MDA: There was effacement of the normal endocervical glandular architecture by a proliferation of well differentiated glands with or without atypia but infiltrative growth. (C)GTA: Glands contain cells with markedly enlarged atypical nuclei and prominent nucleoli.Cells have abundant clear cytoplasm with prominent cell borders. (D)Transitional area between the MDA and GTA components is detected.(N:normal component;M:MDA component;G:GTA component)

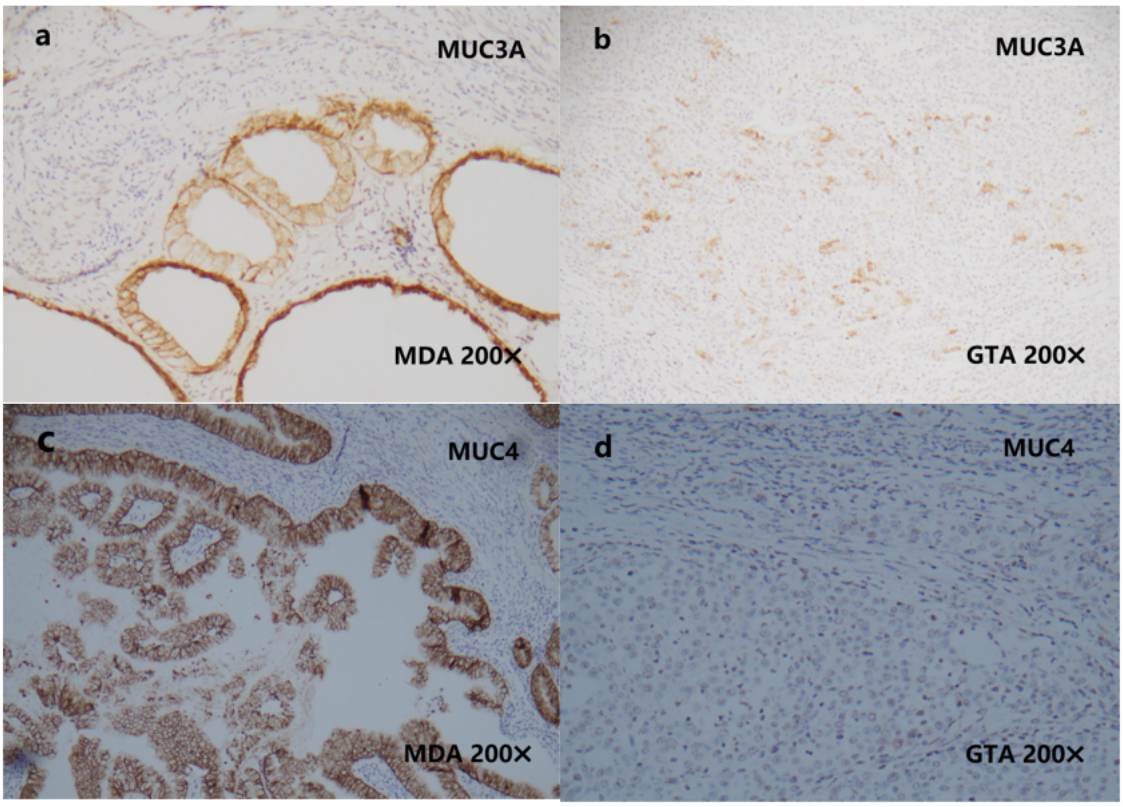

Figure 3

Immunohistochemistry in this case of composite cervical adenocarcinoma. a:Brown staining showed MUC3A was highly expressed in MDA; b:Brown staining showed MUC3A was partially expressed in GTA；c:Brown staining showed MUC4 was highly expressed in MDA; d:Brown staining showed MUC4 was partially expressed in GTA.