Succinate Dehydrogenase Deficient Gastrointestinal Stromal Tumor in a Three Month Old Boy With a Fatal Clinical Course: A Case Report and Review of Literature

Bei-bei lv
Shandong Provincial Hospital https://orcid.org/0000-0003-1972-7245
Jia-Mei Li
shandong provincial hospital
Zhi-Gang Yao
Shandong Provincial Hospital
Xian-Kui Cheng
Shandong Provincial Hospital
Fu-Xin Ren
shandong provincial hospital
Wen-Jing Su
shandong provincial hospital
Ye-Jun Qin
shandong provincial hospital
Zhou Wang (boatw@163.com)
shandong provincial hospital
Zhi-xin Cao
Shandong Provincial Hospital

Case Report

Keywords: SDHB, GIST, Infant, Genetic characteristics, Case report

Posted Date: September 4th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-69380/v1

Version of Record: A version of this preprint was published on February 21st, 2021. See the published version at https://doi.org/10.1186/s13000-021-01077-4.

Abstract

Background: Succinate dehydrogenase deficient gastrointestinal stromal tumors (SDH-deficient GISTs) which lack KIT or PDGFRA mutations demonstrate unique clinical and pathological features, and respond poorly to standard targeted therapy. We herein present a novel case of SDH-deficient GIST in a three-month-old boy in colon mesentery which is the youngest patient until now.

Case presentation: The baby presented with complaints of blood in the stool. CT showed a 6.3×4.6 cm mass in the left lower retroperitoneal. Complete resection of tumor and segmental bowel resection was performed without regional lymphadenectomy. Histologically, tumors are distinctive in their multinodular colon wall involvement with interspersed tracts of colon wall smooth muscle. The tumor was composed mainly of epithelioid cells. Immunohistochemically, the tumor cells were positive for Vim, CD117, PDGFR, while negative for SDHB. Mutational analysis showed a synonymous mutation for SDHB and wild-type for KIT and PDGFRA. Two months after surgery, metastases were found and Imatinib was administered. Unfortunately, the disease continued to progress, the baby died 5 months after surgery.

Conclusions: SDH-deficient GISTs comprise a subgroup of a relatively rare tumor type and show a number of clinically and biologically unique features, especially for infants. It is of great importance to developing new therapeutic targets and novel specific drugs.

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract which have been recognized as a genetically and biologically heterogeneous tumor. Most GISTs harbor activating mutations of KIT or platelet-derived growth factor receptor alpha (PDGFRA) [1]. Approximately 15% of GISTs in adults and more than 90% of pediatric GISTs lack these tyrosine kinase mutations and are generally classified as “wildtype”(WT) GISTs[1-2]. Among them, succinate dehydrogenase (SDH)-deficient GISTs, which are associated with SDH deficiency by immunohistochemistry (IHC), are the largest group [3]. SDH-deficient GISTs occur exclusively in the stomach and are characterized by a distinctive multinodular/plexiform architecture and epithelioid or mixed epithelioid and spindle cell morphology [4-5]. A small subset of patients with SDH-deficient GIST accompanies with Carney-Stratakis syndrome or Carney triad [6]. We herein present a novel case of SDH-deficient GIST in a three-month-old boy in colon mesentery, exhibiting all the clinical, morphological, immunohistochemical, and genetic characteristics of this rare tumor, followed by a brief discussion on this rare entity. To our knowledge, this is the youngest case reported to date.

Case Presentation

A three-month-old baby boy presented with complaints of blood in the stool with a duration of more than half a month. On clinical examination, B-ultrasound results suggested that solid hypoechoic mass was detected in the left lower abdomen, the size was about 6.9×5.0×3.9 cm. Enhanced Computed tomography

(CT) showed a 6.3×4.6cm mass in the left lower retroperitoneal (Fig. 1A). The border is clear, showing uneven reinforcement. No other physical abnormalities were found. Blood routine examination revealed that hemoglobin was 63 g/L and the red blood cell count was 2.15×10^{12}/L. The baby's parents and elder sister are in good health and no related neoplastic lesions were found.

Complete resection of the tumor and segmental bowel resection was performed without regional lymphadenectomy in the pediatric surgery department. The tumor located in the left mesentery with invasion into the colon and sigmoid junction. Adjuvant anti-cancer treatment was not undertaken after the operation on account of bad general condition.

Microscopically, under low magnification, tumors are distinctive in their multinodular colon wall involvement with interspersed tracts of colon wall smooth muscle (Fig. 2A), this is often referred to a “plexiform” pattern as reported before. Under high magnification, the tumor cells have mainly epithelioid cytology with a variably eosinophilic cytoplasm. The nucleus is round or oval, and the nucleolus is obvious. Mitotic images were easy to be seen (Fig. 2B). Lymphovascular and nerve invasion was not found under the microscope.

The panel of immune-histochemical stains included CD117, Dog1, CD34, SDHB, S100, SMA, Desmin, Vim, CD99, Fli-1, Syn, EMA, CDK4, Calponion, WT-1, CR, LCA, Myod1, and Ki67. Among them, Vim, CD117, and PDGFR were diffusely and strongly positive (Fig. 2C, D), which supports the diagnosis of gastrointestinal stromal tumors. Besides, the tumor cells lack SDHB expression, but normal intestinal mucosa and vascular elements were positive which verify adequate immunohistochemical detection (Fig. 2E). The remaining immune markers were negative. The Ki-67 labeling index (MIB-1 index) reached 30% in the area of greatest concentration (Fig. 2F).

Mutational analysis showed a wild-type for KIT and PDGFRA at the five exons examined (KIT exons 9,11,13,17 and PDGFRA exon 18). In addition, all other targets (Her2、EGFR、RET、ROS1、PI3KCA、ALK、KRAS、NRAS and MET) showed no mutation. However, CCND2 amplification and amino acid missense mutation at position 932 of exon 19 of the PTCH1 gene was detected, which may have a significant impact on gene function. At last, we performed SDHB gene sequencing in Jinan Boshang Biotechnology Co. Ltd. Consistent with our expectations, the sequencing of SDHB in tumor showed synonymous mutation at position 169 of exon 1(C-A) (Fig. 3) which may be related to the occurrence and development of this tumor.

On the basis of these findings, the pathological diagnosis of SDH-deficient GIST was established.

Two months later, the baby was brought to our hospital again presented with complaints of cough for two weeks and diarrhea for two days. The results of abdominal color Doppler ultrasound showed that there was much effusion in the abdominal cavity. Abdominal enhanced CT findings suggested that multiple metastases were seen in peritoneum, mesentery, retroperitoneal, left groin and right lower abdominal wall (Fig. 1B). Pulmonary CT suggested double lung inflammatory lesions. Anti-infective treatment was carried out in PICU to correct symptomatic and supportive treatment such as anemia.

When the condition improved, the baby left our hospital. After that his parents visited many other children's hospitals and cancer hospitals, however, no treatment options were acquired. In accordance with the advice of Zhongshan First Affiliated Hospital, Imatinib (100 mg, once daily) was administered. Because of severe diarrhea, the medicine was withdrawal after 3 weeks. Finally, the baby came back to Shandong Provincial Tumor Hospital to take conservative treatment and ascites to relieve bloating symptoms. Unfortunately, the disease continued to progress, the baby died 5 months after surgery.

Discussion

SDH-deficient GISTs represent the largest proportion of WT GISTs which lack KIT or PDGFRA mutations. The true frequency of SDH-deficient GISTs was reported to be approximately 7.4% to 7.7%[6-8]. This group encompasses most pediatric GISTs and two previously described syndromes: Carney-Stratakis syndrome and Carney triad.

Succinate dehydrogenase (SDH) is an enzyme complex composed of four protein subunits (SDHA, SDHB, SDHC and SDHD). This complex acts at the interphase of the tricarboxylic acid cycle and electron transport chain. The SDH-complex participates in the Krebs cycle with subunit A (SDHA) being the catalytic unit responsible for the conversion of succinate to fumarate. Subunit B (SDHB) is an iron-sulfur protein that participates in the electron transport chain for the oxidation of ubiquinone to ubiquinol, and subunits C and D (SDHC and SDHD) are membrane-anchoring subunits. Remarkably, immunohistochemistry for SDHB becomes negative whenever there is bi-allelic inactivation of any component of SDH, which is very rare in the absence of syndromic disease[9]. Loss of SDHB, as tested by immunohistochemistry, is the most practical way to identify SDH-deficient tumors[3,7]. Loss of function of the succinate dehydrogenase complex characterizes a rare group of human tumors including some gastrointestinal stromal tumors, paragangliomas, renal carcinomas, and pituitary adenomas, and these can all be characterized as SDH-deficient tumors [9-10].

SDH-deficient GISTs demonstrate unique clinical and pathological features, including an exclusively gastric location, absence of KIT or PDGFRA mutations, typically showed plexiform muscularis propria involvement and epithelioid hypercellular morphology. Based on current experience, SDH-deficient GISTs occur mainly in the stomach and were more likely to occur in younger, female patients. In this report, we showed a colon mesentery tumor case in a three-month-old boy which was the youngest patient also in an unusual location reported so far[3,7-8,11]. Malignant tumor in infants and young children may represent a different subgroup because of its unique clinical features and biological behavior. The cause of the tumor is unclear. Whether it is associated with embryonic development needs more cases to study.

Histology, SDH-deficient GISTs are characterized by a distinctive multinodular/ plexiform architecture and epithelioid or mixed epithelioid and spindle cell morphology[4]. In our case, “plexiform” pattern is apparent and the tumor cells have mainly epithelioid cytology, which is consistent with the reports before and support for the diagnosis. Not surprisingly, IHC examinations for SDH-deficient GISTs showed positivity for CD117, CD34, DOG-1 and PDGFR, and negativity for SMA and S-100. Loss of SDHB expression is a

consistent feature of SDH-deficient GISTs. The most important molecular change of SDH-deficient GISTs is SDH mutations followed by SDHC promoter hypermethylation[3,12]. SDH mutations are often germline and most commonly A (about 30%), and B, C, or D (together 20%)[3,6,13]. It is unknown how mutations in the various SDH subunits may differentially regulate tumor biology. Patients with alterations of the SDHC gene may be less likely to develop distant metastases[6]. Besides, another feature of SDH-deficient GISTs is overexpression of insulin-like growth factor 1 receptor (IGF1R) gene, possibly by gene amplification. Chou A et al[14]used immunohistochemistry suggested that IGF1R is overexpressed in 100% of SDH-deficient GISTs but never in non-SDH deficient GISTs. In our case, the sequencing of SDHB showed synonymous mutation at position 169 of exon 1(C-A) and the mutation site is in agreement with the results of the previous study[15]. Although amino acid has not changed, synonymous mutation frequently acts as driver mutations in human cancers. Fran Supek et al. present robust statistical evidence in an analysis of > 3,000 cancer exomes and > 300 cancer genomes that synonymous mutations in exons may act through diverse molecular mechanisms, and are often associated with changes in splicing[16]. CCND2 amplification and amino acid missense mutation at position 932 of exon 19 of the PTCH1 gene was found. These novel two changes have not previously been reported in GISTs or other SDH-associated tumors[1,3,10,17]. CCND2 belongs to the highly conserved cyclin family, forms a complex with CDK4 or CDK6 and functions as a regulatory subunit of the complex, whose activity is required for cell cycle G1/S transition. PTCH1 encodes a member of the patched family of proteins and a component of the hedgehog signaling pathway, which is important in embryonic development and tumorigenesis[18]. Whether the changes in these two genes are related to the tumor needs more cases for further study.

SDH-deficient GISTs do not seem to have a marked tendency for familial occurrence, as compared with SDH mutation syndrome associated paragangliomas that show familial occurrence. Due to the rarity of SDH-deficient GISTs, treatment experience is limited especially for pediatric patients. Complete surgical removal of the primary tumor and locoregional (omental or nodal) metastases should be performed whenever possible. There is no uniform about the adjuvant treatment of patients with SDH-deficient GISTs to date. Traditional cytotoxic chemotherapy is generally ineffective for SDH-deficient GISTs, as it is for KIT/PDGFRA mutant GISTs. SDH-deficient GISTs respond poorly to standard targeted therapy such as tyrosine kinase inhibitor drugs, neither the first line inhibitor imatinib mesylate nor a second line multikinase inhibitor sunitinib malate, although stable disease has been observed in some cases[6,8,19]. Newer tyrosine kinase inhibitor drugs are potentially usable in SDH-deficient GISTs include regorafenib, nilotinib, and sorafenib[20]. Better molecular and clinical characterization could improve management.

Conventional risk stratification fails to predict the progression of SDH-deficient GISTs[6]. SDH deficient GISTs run a relatively indolent course despite their frequent lymph node or distant metastasis. Follow-up data shows some patients survived for 10~17 years after peritoneal metastases[7]. However, our case only survived for 5 months after surgery, which may be related to the unique nature of infant and young child malignancies. This case reminds us that such tumors should be vigilant and it is very necessary to collect more cases to study the appropriate treatment.

Conclusions

Consequently, SDH-deficient GISTs comprise a subgroup of a relatively rare tumor type and show a number of clinically and biologically unique features. It is of great importance to developing new therapeutic targets and novel specific drugs. The first priority for further research in this molecular subtype is more extensive sequencing with methods such as whole-exome sequencing, RNA sequencing, and whole-genome sequencing to discover novel genomic events affecting kinases that could suggest therapeutic vulnerabilities. We reported the youngest case of SDH-deficient GIST arising in colon mesentery, and reviewed the relevant literature in order to make a deeper understanding of the disease, and provide useful parameters for further gene therapy.

Abbreviations

GIST: Gastrointestinal stromal tumors; SDH: Succinate dehydrogenase; CT: Computed tomography ; IHC: immunohistochemistry ; WT: wildtype.

Declarations

Acknowledgements

Not applicable.

Author contributions:

Lv BB and Wang Z designed the study; Li JM and Yao ZG acquired clinical data; Su WJ and Cheng XK performed the pathological examination; Ren FX performed the image examination; Lv BB wrote the manuscript; Qin YJ, Wang Z and Cao ZX revised the manuscript. All authors issued final approval for the version to be submitted.

Declarations

Ethics approval and consent to participate

The need for ethics approval and consent was waived, since a consent for publication was obtained from the patient’s parents.

Funding

Supported by the Shandong Province Key R&D Program 2019GSF108268.

Availability of data and materials

All data generated or analyzed during this case are included within the article.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent for publication of the clinical details and/or clinical images was obtained from the parents of the patient. A copy of the consent form is available for review by the Editor of this journal.

References

1. Doyle LA, Hornick JL: Gastrointestinal stromal tumours: from KIT to succinate dehydrogenase. Histopathology 2014;64:53-67.
2. Wang YM, Gu ML, Ji F: Succinate dehydrogenase-deficient gastrointestinal stromal tumors. World J Gastroenterol 2015;21:2303-2314.
3. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, Trent JC, von Mehren M, Wright JA, Schiffman JD, Raygada M, Pacak K, Meltzer PS, Miettinen MM, Stratakis C, Janeway KA, Helman LJ: Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol 2016;2:922-928.
4. Doyle LA, Nelson D, Heinrich MC, Corless CL, Hornick JL: Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumours: a comprehensive genotype-phenotype correlation study. Histopathology 2012;61:801-809.
5. Ibrahim A, Chopra S: Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors. Arch Pathol Lab Med 2020;144:655-660.
6. Mason EF, Hornick JL: Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases. Am J Surg Pathol 2016;40:1616-1621.
7. Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J: Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol 2011;35:1712-1721.
8. Liu W, Zeng X, Wu X, He J, Gao J, Shuai X, Wang G, Zhang P, Tao K: Clinicopathologic study of succinate-dehydrogenase-deficient gastrointestinal stromal tumors: A single-institutional experience in China. Medicine (Baltimore) 2017;96:e7668.
9. Gill AJ: Succinate dehydrogenase (SDH)-deficient neoplasia. Histopathology 2018;72:106-116.
10. Miettinen M: Succinate dehydrogenase-deficient tumors–a novel mechanism of tumor formation. Duodecim 2015;131:2149-2156.
11. Miettinen M, Felisiak-Golabek A, Wang Z, Inaguma S, Lasota J: GIST Manifesting as a Retroperitoneal Tumor: Clinicopathologic Immunohistochemical, and Molecular Genetic Study of 112 Cases. Am J Surg Pathol 2017;41:577-585.

12. Urbini M, Astolfi A, Indio V, Heinrich MC, Corless CL, Nannini M, Ravegnini G, Biasco G, Pantaleo MA: SDHC methylation in gastrointestinal stromal tumors (GIST): a case report. BMC Med Genet 2015;16:87.
13. Dwight T, Benn DE, Clarkson A, Vilain R, Lipton L, Robinson BG, Clifton-Bligh RJ, Gill AJ: Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. Am J Surg Pathol 2013;37:226-233.
14. Chou A, Chen J, Clarkson A, Samra JS, Clifton-Bligh RJ, Hugh TJ, Gill AJ: Succinate dehydrogenase-deficient GISTs are characterized by IGF1R overexpression. Mod Pathol 2012;25:1307-1313.
15. Cheng Y, Zhang Z, Zhu H, Guo L, Cheng Y: Clinicopathologic features of succinate dehydrogenase-deficient gastrointestinal stromal tumor. Zhonghua Bing Li Xue Za Zhi 2016;45:153-158.
16. Supek F, Minana B, Valcarcel J, Gabaldon T, Lehner B: Synonymous mutations frequently act as driver mutations in human cancers. Cell 2014;156:1324-1335.
17. Schaefer IM, Marino-Enriquez A, Fletcher JA: What is New in Gastrointestinal Stromal Tumor? Adv Anat Pathol 2017;24:259-267.
18. Regan JL, Schumacher D, Staudte S, Steffen A, Haybaeck J, Keilholz U, Schweiger C, Golob-Schwarzl N, Mumberg D, Henderson D, Lehrach H, Regenbrecht C, Schafer R, Lange M: Non-Canonical Hedgehog Signaling Is a Positive Regulator of the WNT Pathway and Is Required for the Survival of Colon Cancer Stem Cells. Cell Rep 2017;21:2813-2828.
19. Pantaleo MA, Lolli C, Nannini M, Astolfi A, Indio V, Saponara M, Urbini M, La Rovere S, Gill A, Goldstein D, Ceccarelli C, Santini D, Rossi G, Fiorentino M, Di Scioscio V, Fusaroli P, Mandrioli A, Gatto L, Catena F, Basso U, Ercolani G, Pinna AD, Biasco G: Good survival outcome of metastatic SDH-deficient gastrointestinal stromal tumors harboring SDHA mutations. Genet Med 2015;17:391-395.
20. Miettinen M, Lasota J: Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. Int J Biochem Cell Biol 2014;53:514-519.

Figures

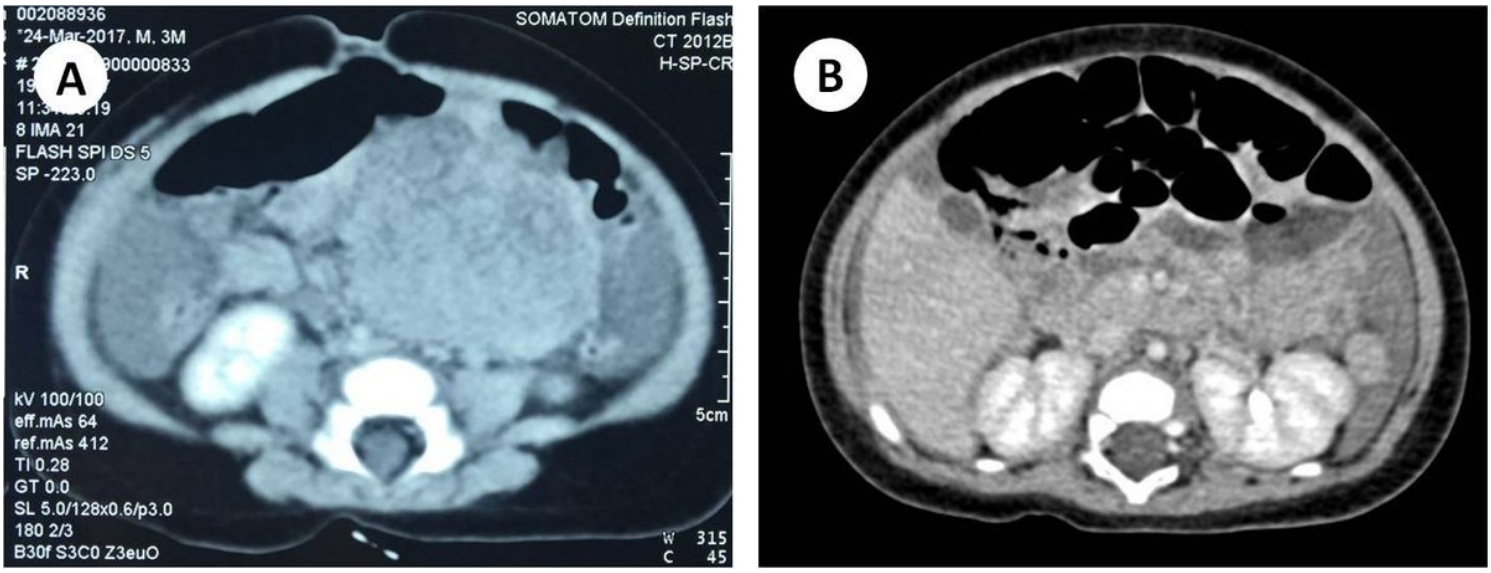

Figure 1

Radiologic findings of the horizontal views. A: Enhanced CT showing a 6.3×4.6cm mass in the left lower retroperitoneal with a clear boarder. B: Enhanced CT findings suggested that multiple metastases were seen in retroperitoneal.

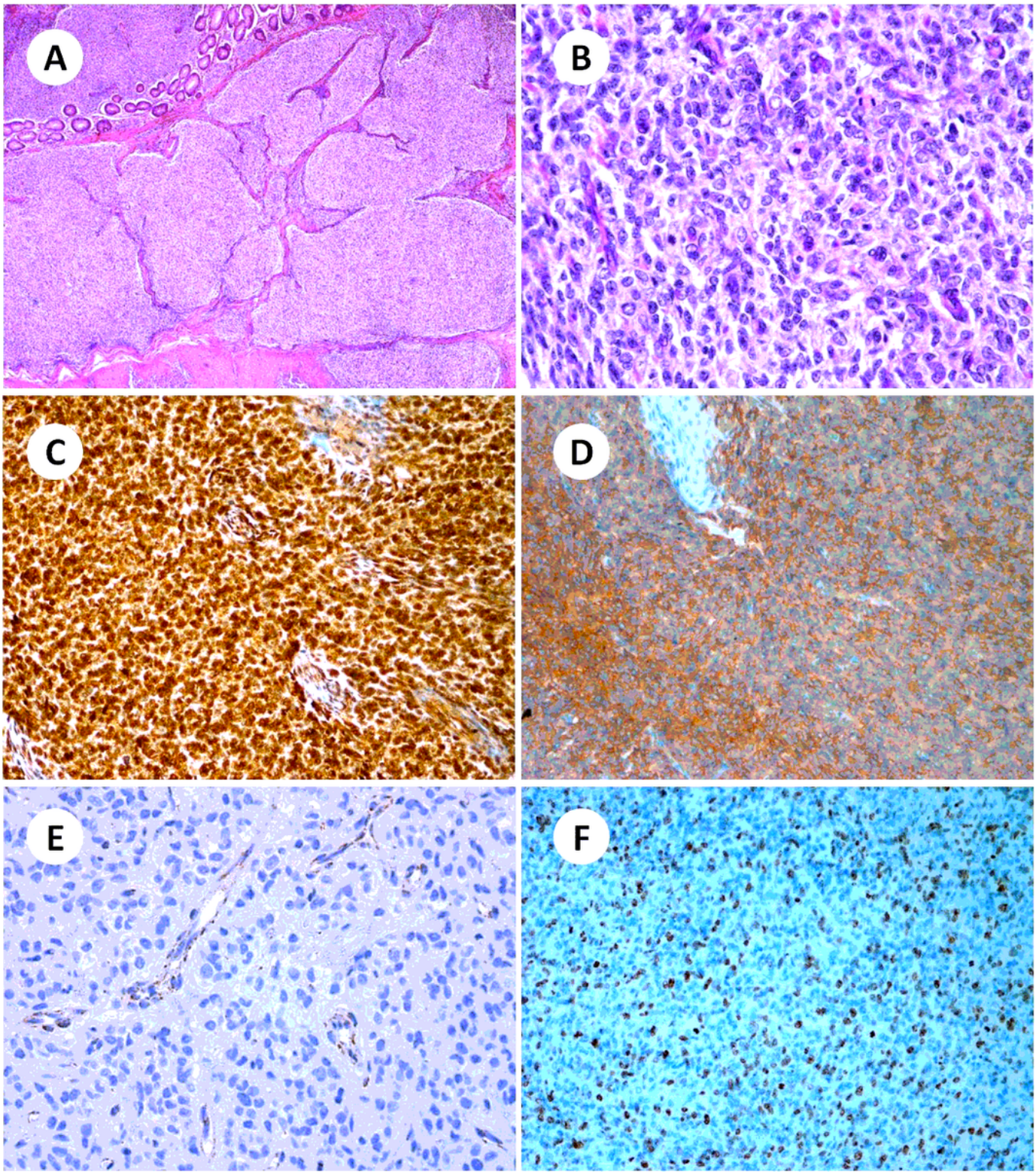

Figure 2

The microscopic features and immunohistochemical stains of the lesion. A: Tumors are distinctive in their multinodular colon wall involvement with interspersed tracts of colon wall smooth muscle (H&E, ×100). B: The tumor cells have a mainly epithelioid cytology with variably eosinophilic cytoplasm. Mitotic images were easy to be seen (H&E, ×400). C: PDGFR was diffusely and strongly positive (×200). D: The tumor cells were positive for CD117 (×200). E: The tumor cells lack SDHB expression, but vascular

elements were positive (×400). F: The Ki-67 labelling index (MIB-1 index) reached 30% in the area of greatest concentration (×200).

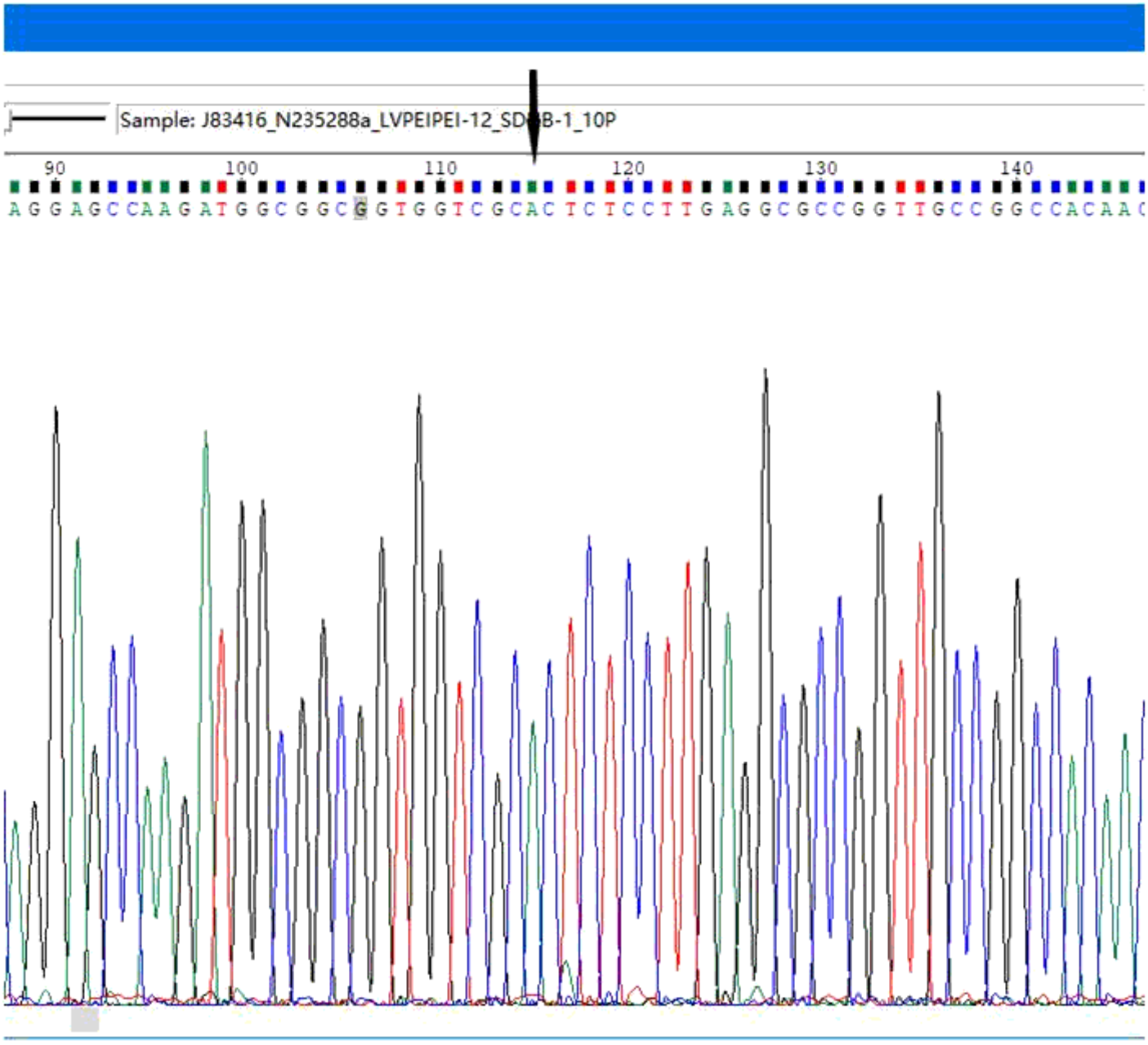

Figure 3

Sequencing results shows mutation at position 169 of exon 1(C-A) (shows mutated loci.)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- NEWCAREchecklistEnglish2013.pdf