Cronkhite-Canada syndrome complicated with three malignant tumors: a case report and whole exome sequencing analysis

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To the Editor: Cronkhite-Canada syndrome (CCS) is a rare, non-hereditary disease characterized by diffuse gastrointestinal polyposis and ectodermal abnormalities.[1] Although CCS polyps are not considered to be neoplastic, 15% to 25% patients have been documented with colorectal or gastric cancer at diagnosis, and up to 40% of patients have been documented with adenomas and adenomatous changes.[2] Extra-gastrointestinal neoplasms have been sporadically reported, but their association with CCS remains under investigation. The underlying mechanism of CCS has been less investigated, with only one whole exome sequencing (WES) study that identified a protein kinase DNA-activated catalytic subunit (PRKDC) DNA variant that might contribute to the pathogenesis.[3] Here, we report a case of CCS that was complicated with three malignant tumors. WES analysis of this case identified certain germline mutations that might provide insight into the pathogenesis. This study was approved by the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences (No. ZS-1725).

A Chinese male patient at the age of 46 years was first admitted to our hospital for diarrhea, alopecia, nail separation, and skin hyperpigmentation over a period of 4 months. He was diagnosed with CCS and concurrent colonic adenocarcinoma. Endoscopy at follow-up showed multiple polyps lining the stomach [Figure 1A] and colon [Figure 1B]. The patient was detected with spermatogonia at the age of 30 years and small cell lung cancer at the age of 58 years. Additionally, he had a family history of gastric cancer affecting his father and sister.

The coexistence of complex cancer history and CCS made this patient an interesting rare case. Therefore, WES analysis was considered to explore whether some germline mutations may account for the susceptibility to CCS and concurrent malignancies. DNA samples of this patient were sequenced on the Illumina HiSeq 2500 platform (Illumina, San Diego, CA, USA) using pair-end method with a sequencing depth of 50×. The germline mutations identified by WES were listed in Supplementary Table 1, http://links.lww.com/CM9/A111. Rare missense mutations with a frequency <0.05 were selected for further analysis according to the 1000genome-eas (http://www.internationalgenome.org/category/population/) and ExAC (http://exac.broadinstitute.org) databases. GeneCodis3 (http://genecodis.cnb.csic.es/analysis) was used to designate the functional annotations to genes that contain more than one rare missense mutation. A total of 814 variants in 625 genes were identified, among which 37 genes have two rare missense mutations and 24 genes have more than three missense mutations. Functional annotations of the above genes identified nine genes related to known diseases [Supplementary Table 2, http://links.lww.com/CM9/A111]. Further literature search indicated that *MUC3A* (OMIM: 158371) and *MUC5B* (OMIM: 600770) may be involved in the pathogenesis of both inflammatory diseases and cancers.[4,5] Bioinformatics analysis predicted that the mutations in *MUC3A* may lead to changes in its O-glycosylation site and phosphorylation site. However, the mutations in *MUC5B* was not predicted to cause changes in protein structure and function. Immunohistochemical staining in the gastric hyperplastic polyps of this patient showed reduced MUC3A expression compared to normal mucosa when MUC1 and MUC2 expression remain unchanged [Figure 1C–H].

In conclusion, we described a case of CCS who was complicated with colonic adenocarcinoma, seminoma, and small cell lung cancer. Germline mutations of *MUC3A* and reduced MUC3A protein in hyperplastic polyps might

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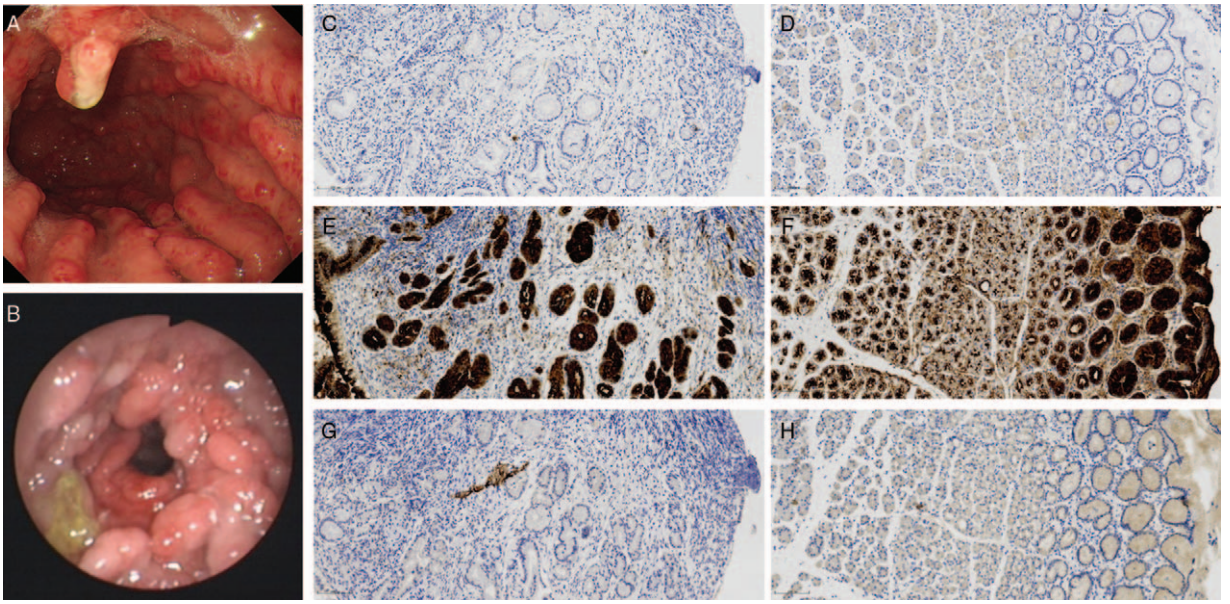

Figure 1: Endoscopic features (A, B) and immunohistochemical staining (C–H) of the patient. (A) Multiple polyps lining the stomach; (B) Multiple polyps lining the colon; (C) Reduced MUC3A expression of gastric hyperplastic polyps; (D) MUC3A staining of normal gastric mucosa; (E) Normal MUC1 expression of gastric hyperplastic polyps; (F) MUC1 staining of normal gastric mucosa; (G) Normal MUC2 expression of gastric hyperplastic polyps; (H) MUC2 staining of normal gastric mucosa (C–H: original magnification ×20).

contribute to the pathogenesis of this patient. Further investigation of germline and somatic mutations in more CCS patients is needed to elucidate the molecular landscape of this disease and provide more insights for the concurrent carcinogenesis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the article. The patient understands that his name and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

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