Author’s response to reviews

Title: Development of metachronous rectal cancers in a young man with dyskeratosis congenita: A case report

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Response to Reviewers

First of all, we are grateful to the reviewers for critical comments and invaluable suggestions that have helped us to improve our manuscript. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.
Reviewer: 1

Comments to the Author

1) This case report is very important because the author can reveal the cancer-related germline mutation in the case with dyskeratosis congenita. This information will contribute the method to follow the case like this. However, this report did not reveal the clinical information regarding the rectal cancers. The authors should reveal the endoscopic findings in each 16 and 18 years. If the endoscopic findings were specific, please clarify the findings in each time. Furthermore, the authors should reveal the histological findings of this case.

Response

We added the endoscopic and histological images in figure 1 and described these findings in page 6 and 7 as follows.

endoscopic examination showed ulcerative tumor in the rectum (Fig.1a)
Tumor was a protruding 2.8 cm×2.5 cm mass in rectum with well or moderate differentiation and full thickness infiltration (pT4N1M0, Stage IIIB).

endoscopic examination showed superficial elevated tumor in the rectum (Fig.1c).
Tumor was a protruding 3.5 cm×1.5 cm mass in rectum with well or moderate differentiation (Fig.1d) and submucosal infiltration (pT1N0M0, Stage I).

Reviewer: 2

Comments to the Author

I have following minor suggestions to the authors,
1. Background: Page 5.

- Please describe the Dyskeratosis congenita (DC) more elaborately including some historical background and provide references if needed. Provide clinical features of the DC (Major vs. Minor) and its transmission and almost exclusive occurrence in males.

- Please provide details on the previously reported cases of rectal cancer in DC. Including any epidemiological data if available.

Response

We added description about historical background and clinical features of DC in page 5 and 6 and introduced one DC cases with rectal cancer reported from Japan in page 9 as follows.

In page 5 and 6,

Dyskeratosis congenita (DC) which is also known as Zinsser-Cole-Engman syndrome originally reported by Zinsser in 1906 [1]

At least two features of them or one feature plus two or more following findings suspect DC; eye abnormalities (epiphora, blepharitis, sparse eyelashes, ectropion, entropion, trichiasis), dental abnormalities (caries, periodontal disease, taurodontism), alopecia, developmental delay, short stature, microcephaly, hypogonadism, esophageal stenosis, urethral stenosis, liver disease, osteoporosis and avascular necrosis of the hips or shoulders [2].
However, the mode of inheritance of DC varies by genes, TERC and TINF2 demonstrate autosomal dominant (AD) and CTC1, NHP2, NOP10, PARN and WRAP53 autosomal recessive (AR). RTEL1, TERT and ACD show AD or AR manner. DKC1 is a causative gene for X-linked recessive inheritance of DC (MIM305000) [8][9][10]. In this case, only male affects DC, in general.

In page 9

One DC patient having rectal cancer have been reported from Japan. A 24-year-old Japanese man with DC complicated by non-cirrhotic portal hypertension, signet ring carcinoma of the rectum and Pneumocystis carinii pneumonia [18].

2. Case presentation: Page 6

-Please provide any pathological slides on the tumor which resected at age 18.

Response

We added the pathological slides in Figure 1.

-Please mention if the patient had any relevant social history. If negative, say so.

It's important to know if the patient had any carcinogenic habits or practices such as smoking, alcohol, or unprotected sun exposure.
Response

We described the relevant social history in page 7 as follows.

He had no smoking and drinking habit. His two brothers and parents had no symptoms. His parents are not consanguineous marriage.

- If possible, please define what Microsatellite instability is and then report its results.

Response

We described about microsatellite instability and its meaning in page 7 and 8 as follows.

Since this patient developed juvenile-onset multiple rectal cancers and hematological malignancy, we suspected constitutive mismatch repair deficiency (CMMRD) syndrome, which is a childhood cancer predisposition syndrome especially brain tumor, colorectal tumor and hematological malignancies, involving biallelic germline pathogenic variants of MMR genes. However, microsatellite instability (MSI) testing with tumor tissue demonstrated MSI-low indicating the possibility of MMRD is low.

Reviewer: 3

Comments to the Author

Well written and investigated.

1. Can authors provide the radiological imaging and endoscopic findings that where was the location of the tumour on endoscopy/MRI?
Response

We added radiological and endoscopic images in Figure 1 and 2 and described endoscopic in page 6 and 7 findings as follows.

endoscopic examination showed ulcerative tumor in the rectum (Fig.1a).
Tumor was a protruding 2.8 cm×2.5 cm mass in rectum with well or moderate differentiation and full thickness infiltration (pT4N1M0, Stage IIIB).

endoscopic examination showed superficial elevated tumor in the rectum (Fig.1c).
Tumor was a protruding 3.5 cm×1.5 cm mass in rectum with well or moderate differentiation (Fig.1d) and submucosal infiltration (pT1N0M0, Stage I).

2. Staging of the tumour included multiple classifications, as authors have used combination of Japanese and TNM classifications. So, it should be clarified further for better understanding of readers.

Response

We unified staging TNM classification as described above. (page 7)

3. Authors have advised for "appropriate surveillance". Authors have reviewed it extensively, what should be optimum time for starting surveillance and methods of surveillance? This should be included in the discussion.

Response

We described about surveillance in page 10 as follows.

therefore, appropriate surveillance may be required, such as fecal occult blood test, digital rectal examination and/or endoscopic examination from the age of 10, considering this case.