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Letter to the Editor

Neoplasms and Chemotherapy Side Effects in MELAS Patients are Likely Associated with the Underlying Genetic Defect

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We read with interest the article by Kawakubo *et al.* regarding a 40-year-old female patient with MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) caused by the m.3243A>G variant. She developed severe enteritis as a side effect of CapeOX therapy for metastatic colorectal carcinoma [1]. The symptoms of enteritis improved after discontinuation of this adjuvant chemotherapy [1]. Although the study is noteworthy, several points warrant discussion.

First, the key determinants of the phenotype were not investigated [1]. In addition to heteroplasmy, information regarding mtDNA copy number, haplogroup, the threshold effect, mitotic segregation, tissue energy demand, nuclear-mitochondrial genome interactions, the nature and extent of the mutation, age and sex, environmental toxins, mitochondrial-toxic drugs, diet, and physiological oxidative stress would be of interest, potentially to explain the development of the malignancy [2].

Second, there is a lack of information regarding family history [1]. Since mtDNA variants are transmitted via the maternal line and inherited from the mother in 75% of cases [3], it is highly probable that the index patient's mother or other first-degree relatives also carried the m.3243A>G variant and were clinically or subclinically affected by the disease. Knowing which family members are mutation carriers and which are not is crucial for genetic counseling and for understanding how the variant segregated within the family and whether phenotypic heterogeneity existed among the affected family members.

A third point is that the criteria used to diagnose MELAS in the index patient were not reported [1]. MELAS is typically diagnosed based on the Hirano criteria, the Japanese criteria, or the Pavlakis criteria [4, 5, 6]. Did the patient actually meet any of these criteria? Of particular importance is the question of whether the patient ever experienced a stroke-like episode, the hallmark feature of MELAS.

A fourth point is that the phenotype was not described in detail [1]. The m.3243A>G variant frequently manifests phenotypically as a multisystem disorder affecting the brain, eyes, ears, vestibular system, endocrine system, heart, gastrointestinal tract, hematological system, skin, or immune system. Was the patient systematically examined for abnormalities in these organ systems?

A fifth point is that gastrointestinal disorders can manifest in carriers of the m.3243A>G variant [7]. Did the patient have pre-existing gastrointestinal complaints, or did she develop other side effects from the chemotherapy?

A sixth point is that there is evidence suggesting a generally increased rate of neoplasms in mitochondrial disorders (MIDs). Did the patient present with risk factors for the development of a colorectal neoplasm?

Finally, the long-term clinical course was not reported. Did the patient survive, did she receive further cancer therapies, and what was the status of the liver metastases? Was further adjuvant chemotherapy attempted after the discontinuation of CapeOX?

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1. Kawakubo H, Ryu S, Imaizumi Y, Suzuki D, Nakashima S, Goto K, *et al.* A case of severe enteritis following CapeOX therapy in a postoperative rectal cancer patient with m.3243A>G-associated mitochondrial disease. *Int Cancer Conf J*, Aug 25, 2026; 15(4):568-574. Doi: 10.1007/s13691-026-00901-2
2. Shi Y, Chen G, Sun D, Hu C, Liu Z, Shen D, *et al.* Phenotypes and genotypes of mitochondrial diseases with mtDNA variations in Chinese children: A multi-center study. *Mitochondrion*, Jan 2022; 62:139-150. Doi: 10.1016/j.mito.2021.11.006
3. Poulton J, Finsterer J, Yu-Wai-Man P. Genetic Counselling for Maternally Inherited Mitochondrial Disorders. *Mol Diagn Ther*, Aug 2017; 21(4):419-429. Doi: 10.1007/s40291-017-0279-7
4. Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, *et al.* MELAS: A nationwide prospective cohort study of 96 patients in Japan. *Biochim Biophys Acta*, May 2012; 1820(5):619-624. Doi: 10.1016/j.bbagen.2011.03.015
5. Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, *et al.* Melas: An original case and clinical criteria for diagnosis. *Neuromuscul Disord*. 1992; 2(2):125-135. Doi: 10.1016/0960-8966(92)90045-8
6. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: A distinctive clinical syndrome. *Ann Neurol*, Oct 1984; 16(4):481-488. Doi: 10.1002/ana.410160409

7. Finsterer J, Strobl W. Gastrointestinal involvement in neuromuscular disorders. *J Gastroenterol Hepatol*, Oct 2024; 39(10):1982-1993. Doi: 10.1111/jgh.16650