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Re: Renal medullary carcinoma and its association with sickle cell trait: a case report and literature review

The Editor
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We read with great interest the article by Holland *et al.*[1] in which the authors report a case of renal medullary carcinoma (RMC) with long survival, its association with sickle trait, and a revision of the pertinent literature.

In their case, based on pathology analysis, the authors concluded for a "pT3aN1 cancer." Then "after further history, the patient reported Greek heritage and a family history of sickle cell anemia." Hemoglobin electrophoresis was performed and revealed "hemoglobin S quantification of 38%," a finding consistent with sickle cell trait. Based on the new information, "a diagnosis of RMC was made."

We were surprised that no mention of the erythrocyte shape was made in their detailed description of the morphologic and immunohistochemical features of the tumour. Sickled erythrocytes are notoriously promptly detectable in tumour sections from RMC nephrectomy[2].

Renal medullary carcinoma is a rare and aggressive high-grade renal cell carcinoma exclusively affecting young patients with sickle cell trait or, in the very few remaining cases, with other sickle hemoglobinopathies including sickle cell disease, sickle cell hemoglobin C, and sickle beta thalassemia[2–4]. Its development outside that context is controversial. Indeed, in the 4th edition of the World Health Organization's *Classification of Tumours of the Urinary System and Male Genital Organs*[4], high-grade renal cell carcinoma with "morphology and immunophenotypic or molecular characteristic identical to those of medullary carcinoma," but occurring in a patient without evidence of a sickle hemoglobinopathy is recommended to be diagnosed as "unclassified renal cell carcinoma with renal medullary phenotype." But if tumour morphology has a sense for diagnosis (that is, high-grade renal cell carcinoma with a medullary phenotype), does erythrocyte morphology have a sense for nosology?

Even though family history and hemoglobin electrophoresis are outstanding tools to resolve the correct nosology of a renal cell carcinoma with "renal medullary phenotype"[3,4], we feel that morphologic evaluation of the erythrocytes in tumour sections has the same importance. Indeed, only erythrocytes that contain hemoglobin S can, in a hypoxic microenvironment, sickle, and RMC is a tumour specifically associated with sickle hemoglobinopathies[1–4]. In addition, the "regional ischemia due to reduced blood flow and increased viscosity" that results from sickling of erythrocytes in the vasa recta of the renal inner medulla, which is the most hypoxic region in the human body, has been proposed as a leading mechanism in the pathogenesis of RMC[5]. Thus, sickled erythrocytes have to be carefully sought in the histology sections from a tumour having features consistent with RMC. Their morphologic identification allows to establish the existence of an unknown sickle hemoglobinopathy (to be defined precisely by knowledge of the clinical history of the patient or by hemoglobin electrophoresis if the patient's clinical history is negative) and to classify the tumor as RMC.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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