A female patient in her early 20s presented with a recent history of cough and weight loss.Computed tomography imaging revealed a mediastinal mass and findings concerning for metastatic disease, including involvement of the lungs and bone.

A biopsy of a supraclavicular lymph node was performed. Histopathologic examination revealed a high-grade malignant neoplasm (Figure 1A) with diffuse positivity for PAX8, raising the possibility of metastatic renal cell carcinoma (RCC). Further work-up revealed loss of SMARCB1/INI-1 expression (Figure 1B), which is seen in renal medullary carcinoma. In addition, this tumor exhibited loss of fumarate hydratase and aberrantly high levels of S-(2-succino)-cysteine (Figure 1C and D), which is seen in hereditary leiomyomatosis and renal cell cancer (HLRCC)—associated RCC.

Which of the following findings would be expected in a patient with renal medullary carcinoma?

a. No association with either OCT3/4 expression or hemoglobinopathy
b. Absent expression of OCT3/4 and presence of an underlying hemoglobinopathy

(see page 631 for answer)
c. Positive expression of OCT3/4 and an underlying hemoglobinopathy

d. Positive expression of OCT3/4 without an underlying hemoglobinopathy

Answer: c. Positive expression of OCT3/4 and an underlying hemoglobinopathy

Both renal medullary carcinoma and HLRCC-associated RCC tend to have a younger age at onset.1,2 HLRCC-associated RCC occurs secondary to pathogenic germline alterations of the fumarate hydratase (\textit{FH}) gene, and the spectrum of associated neoplasia includes uterine and cutaneous leiomyomas and renal tumors. Immunohistochemistry frequently shows loss of fumarate hydratase and increased \textit{S}-(2-succinio)cysteine in most of these tumors, with rare exceptions, and therefore can serve as a diagnostic tool to establish a diagnosis of a fumarate hydratase–deficient tumor.2 Renal medullary carcinoma is frequently seen in patients with sickle cell trait.1 Most of these tumors express OCT3/4 and show loss of SMARCB1/INI-1 (a constituent of the SWI/SNF chromatin remodeling complex).1,3 In routine clinical practice, loss of SMARCB1/INI-1 is used to establish a diagnosis of renal medullary carcinoma.

Recent work by The Cancer Genome Atlas has revealed a “CpG island methylator phenotype (CIMP)” in a subset of papillary RCC “characterized by poor survival and mutation of the gene encoding fumarate hydratase.”4 We hypothesize that RCC with \textit{FH} mutations and the CIMP phenotype may show epigenetic silencing of members of the SWI/SNF chromatin remodeling complex. In this context, a study has found that close to 10% of FH-deficient RCCs exhibit loss of members of the SWI/SNF chromatin remodeling complex, probably secondary to epigenetic mechanisms.5 This included a report of a single case of an FH-deficient RCC, with concurrent loss of SMARCB1/INI-1, like the immunophenotype seen in our report.5

This tumor showed an absence of OCT3/4 expression (Figure 2). Although no relevant personal or family history of neoplasia was present in this case, follow-up testing confirmed absence of an underlying hemoglobinopathy and revealed the presence of a likely pathogenic germline alteration of the \textit{FH} gene (\textit{FH} \textit{p.H135R}).
REFERENCES


