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Case study

Clear cell renal cell carcinoma with intratumoral and nodal extramedullary megakaryopoiesis: a potential diagnostic pitfall

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Summary Clear cell renal cell carcinoma is occasionally associated with erythrocytosis, hypothesized to result from tumoral production of erythropoietin. Rarely, intratumoral erythropoiesis has been identified, although intratumoral megakaryopoiesis has not, to our knowledge, been previously described. We report the case of an 81-year-old man with myelofibrosis who underwent resection of a 9.8-cm clear cell renal cell carcinoma. Numerous megakaryocytes were present within the renal cell carcinoma; regional lymph nodes; and, to a lesser extent, the nonneoplastic kidney, glomeruli, and renal hilar soft tissue, in some areas associated with trilineage hematopoiesis. Immunohistochemistry verified the megakaryocytic lineage of the atypical cells (CD61, CD42b, and von Willebrand factor +; cytokeratin −). Intratumoral extramedullary megakaryopoiesis is a novel finding in clear cell renal cell carcinoma with potential to mimic high-grade carcinoma and involvement of lymph nodes. Careful attention to morphology, presence of other hematopoietic elements, and immunoprofile can facilitate recognition of this rare phenomenon.

1. Introduction

Unique clinicopathological features of clear cell renal cell carcinoma include an occasional association with erythrocytosis, thought to result from production of erythropoietin by tumor cells [1,2]. Despite this association, foci of intratumoral erythropoiesis are rarely conspicuous [3,4]. In the setting of myelofibrosis, extramedullary hematopoiesis within the nonneoplastic kidney has been rarely reported, sometimes forming a mass-like lesion [5-7]. However, intratumoral megakaryopoiesis within clear cell renal cell carcinoma has not, to our knowledge, been previously reported. Because tumor cells with bizarre, irregular, or multilobed nuclei are indicative of the highest nuclear grade in clear cell renal cell carcinoma (Fuhrman grade 4) [8] and involvement of regional lymph nodes by similar cells would suggest the presence of metastatic carcinoma, intratumoral and nodal megakaryopoiesis has the potential to be a substantial diagnostic pitfall. In this article, we report the case of an 81-year-old man with clinical history of

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myelofibrosis who presented with a large renal mass. Florid extramedullary megakaryopoiesis was present within the clear cell renal cell carcinoma and regional lymph nodes, mimicking high-grade tumor cells and lymph node metastases, respectively. Less conspicuous foci of extramedullary trilineage hematopoiesis were also present within the nonneoplastic kidney, lymph nodes, and renal hilar soft tissue, representing a diagnostic clue to the true nature of the large, atypical cells.

2. Materials and methods

2.1. Case report

An 81-year-old man presented for urologic evaluation after identification of a large, right-sided renal mass. A reported clinical history of myelofibrosis was noted, associated with hepatosplenomegaly. Recent peripheral blood examination yielded a white blood cell count of 41.6 k/mm^3, hemoglobin level of 9.7 g/dL, hematocrit of 28%, and platelet count of 158 k/mm^3. Review of the peripheral blood smear demonstrated a leukoerythroblastic picture with circulating immature myeloid cells, nucleated red blood cells, and large platelets. Unfortunately, bone marrow examination confirming a hematopathologic diagnosis of primary myelofibrosis and other studies, including *JAK2* mutational analysis, were not available for review. Radical nephrectomy with retroperitoneal lymph node dissection was performed.

2.2. Methods

Four-micrometer sections were prepared from the radical nephrectomy specimen and regional lymph nodes for hematoxylin and eosin staining and immunohistochemistry. Immunohistochemical staining with antibodies directed against CD34 (Dako, Carpinteria, CA), CD42b (Novocastra, Newcastle Upon Tyne, UK), CD61 (Cell Marque, Rocklin, CA), cytokeratin AE1/AE3 (Dako), glycophorin A (Dako), myeloperoxidase (Dako), and von Willebrand factor (Dako) was performed in an automated Dako instrument with appropriately reacting positive and negative controls.

3. Results

Grossly, the radical nephrectomy specimen contained a 9.8 × 9.5 × 6.0 cm variegated, hemorrhagic, tan, golden yellow, and red-brown mass with areas of calcification. Interaortocaval and paracaval lymph node dissection specimens contained 6 lymph nodes, ranging in size from 1.0 to 2.5 cm. Microscopically, the renal neoplasm was composed of nests and alveolar structures, lined by cells with voluminous clear cytoplasm. Large zones were composed of hyaline scar, hemorrhage, and calcification. Scattered throughout the neoplasm were numerous megakaryocytes (within the lumina of the alveolar structures, admixed with the epithelial cells, and in the fibrovascular network surrounding the tumor cell nests), characterized by voluminous eosinophilic cytoplasm and large, irregular, multilobed, hyperchromatic nuclei (Fig. A and B). Erythropoiesis was focally present within the tumor, and trilineage hematopoiesis could be identified in hilar soft tissue and the renal parenchyma (Fig. C and D). Rare, large hyperchromatic nuclei could be appreciated within glomeruli, suggesting the presence of intraglomerular entrapped megakaryocytes.

Regional lymph nodes also contained multifocal extramedullary hematopoiesis, most prominently megakaryopoiesis (Fig. E). Immunohistochemical staining revealed the intratumoral megakaryocytes to be negative for cytokeratin AE1/AE3 and positive for CD42b, CD61, and von Willebrand factor (Fig. B, inset). A few of the rare large cells within glomeruli were highlighted by immunohistochemistry for CD61 (Fig. F). Staining for glycophorin A labeled the foci of erythropoiesis (Fig. C, inset) and antibodies to myeloperoxidase labeled myeloid precursor cells (Fig. D, inset). Staining for cytokeratin AE1/AE3 labeled only the nonneoplastic renal tubules in these areas. Antibody to CD34 did not reveal aggregates of hematopoietic blasts.

4. Discussion

Extramedullary hematopoiesis is characteristically observed when the ability to carry out trilineage hematopoiesis in the bone marrow is restricted secondary to space-occupying abnormalities, such as increased marrow fibrosis. Sites commonly involved include liver, spleen, and lymph nodes [3,4]. Despite the association of clear cell renal cell carcinoma with erythrocytosis and production of erythropoietin [1,2], intratumoral erythropoiesis appears to be distinctly uncommon [3,4], and prominent intratumoral megakaryopoiesis has, to our knowledge, never been previously reported.

In other organs, the ability of nodal megakaryopoiesis to mimic metastatic tumor cells has been occasionally noted, such as in breast cancer sentinel lymph nodes [9,10] or regional lymph nodes from Wilms tumor resection specimens [11], although similar megakaryopoiesis has not been noted within the tumors themselves. Likewise, we have encountered extramedullary megakaryopoiesis in lymphadenectomy specimens for other malignancies, including prostate cancer and testicular germ cell tumor (unpublished observations). However, in most of these settings, the primary tumors typically lack severe nuclear atypia or anaplasia that would be necessary to confuse megakaryocytes with tumor cells. A small subset of solid tumors has been reported to contain foci of extramedullary hematopoiesis, such as hepatic angiomyolipoma, liposarcoma, spindle