Leukocytosis, thrombocytosis and hypercalcemia as a triple paraneoplastic syndrome in a patient with squamous cell carcinoma of the renal pelvis

Renal yassı hücreli karsinomda multiple pareneoplatik sendrom olarak lökositoz, trombositoz ve hiperkalsemi

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To the Editor,

Squamous cell carcinoma (SCC) of the renal pelvis is a rare malignancy [1]. Paraneoplastic syndromes are common; however, multiple paraneoplastic syndromes are rarely observed. We describe a case with triple paraneoplastic syndrome including hypercalcemia, leukocytosis and thrombocytosis as multiple hematological paraneoplastic syndromes in a patient with renal pelvis SCC.

A 58-year-old male patient was admitted to clinic because of right flank pain, nausea, vomiting, and constipation. He underwent a right nephrectomy four months before and diagnosis of SCC of the renal pelvis was established. Invasion of the renal capsule and adipose tissue was seen with negative surgical border. On admission, he was clinically deteriorated. He had anemia (hemoglobin 9 mg/dl), leukocytosis (WBC 57.6 x 10^9/L) and thrombocytosis (576 x 109/L). Leukocyte differential count showed 85% neutrophil, 20% lymphocyte, 7% monocytes, and 1% eosinophil, respectively. Serum creatinine, calcium and parathyroid hormone levels were 2.6 g/dl (range: 0.5-1.2 mg/dl), 14 mg/dl (range: 8.8-10.8 mg/dl) and 6.47 pg/ml (range: 15-65 pg/ml), respectively. Abdominal ultrasound revealed hypoechogenic lesions in the left renal region, multiple metastases of the liver. Fine needle aspiration from the mass revealed SCC. Treatment to correct hypercalcemia was started with saline hydration, furosemide and, zoledronate. Thorax computerized tomography and bone scan were negative for metastasis. Peripheral blood smear, bone marrow aspiration and biopsy showed no pathologic finding regarding any hematologic disorder, bone marrow metastasis or infectious disease. Unfortunately, we did not perform leukocyte alkaline phosphatase (LAP) stain or analysis of Philadelphia chromosome. Cisplatin and etoposide combination regimen was administered to the patient. Performance status of the patient decreased after two cycles of chemotherapy. Objective response was not observed. The patient died in four months with progressive disease. Hypercalcemia was under control with bisphosphonate but hematological findings continued.

Squamous cell carcinoma of the renal pelvis is rare and accounts for less than 1% of urological malignancies [1]. It has poor prognosis with a median survival of 3.5 months. Coexisting urinary stone and carcinoma ranges from 18 to 100% [2].

Paraneoplastic syndrome has a very wide spectrum, from simple clinical events such as fever to complex clinical syndrome. Many different mechanisms may play a role in the pathogenesis of paraneoplastic syndrome, such as cytokines, hormones, and autoimmunity, etc. Hypercalcemia is more common in squamous histology than other histopathological subtypes [3]. Hypercalcemia has two different mechanisms: one is paraneoplastic syndrome and the other is involvement of bone. Paraneoplastic

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hypercalcemia is closely associated with parathyroid hormone-related peptide and interleukin-6 [4]. Hematologic paraneoplastic syndromes have a wide spectrum, from coagulopathy to abnormality of blood cells, granulocyte colony-stimulating factor (G-CSF) is a major component of the mechanism in leukocytosis [5]. Dukes et al. [6] reported paraneoplastic leukemoid reaction as a marker for transitional cell carcinoma recurrence. They indicated the role of G-CSF in their case. Thrombocytosis can occur by complex multiple mechanisms or thrombopoietin which has a major hematologic growth factor effect on platelet development map play role.

Combination of paraneoplastic syndromes is a seldom clinical feature. Double paraneoplastic syndromes are relatively common. Triple or more paraneoplastic syndrome is highly interesting. Paraneoplastic syndrome of leukocytosis, thrombocytosis and hypercalcemia associated with SCC of the skin was reported [7]. There is little published data in the literature about paraneoplastic syndrome occurring in renal pelvic carcinoma [3]. Hypercalcemia and other hematological paraneoplastic syndromes had been reported [8]. A triple paraneoplastic syndrome in a patient with renal squamous cell carcinoma had been reported by Er et al. previously [9]. We describe here in a new patient who had the same features including hypercalcemia, leukocytosis and thrombocytosis in renal SCC. We were not able to show any cytokines-, growth factor-or hormone-associated pathogenesis in the clinical management. We conclude that many of the factors discussed in the literature, such as parathyroid hormone-related peptide and G-CSF, may be underlying factors in the pathogenesis in our case.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

References

1. Kose F, Bal N, Ozyilkan O. Squamous cell carcinoma of the renal pelvis. Med Oncol 2009;26:103-4.
2. Holmäng S, Lele SM, Johansson SL. Squamous cell carcinoma of the renal pelvis and ureter: incidence, symptoms, treatment and outcome. Urol 2007;78:51-6.
3. Walls J, Bundred NJ. Squamous cell carcinoma of the renal pelvis associated with urinary diversion and humoral hypercalcaemic malignancy syndrome. J R Coll Surg Edinb 1992;37:207-8.
4. Takaoka S, Yamane Y, Nishiki M, Yamaguchi T, Sugimoto T. Primary pulmonary squamous cell carcinoma associated with elevated IL-6, leukocytosis, hypercalcemia, phagocytosis, reactive lymphadenopathy and glomerular mesangial cell proliferation via the production of PTH-rP and G-CSF. Intern Med 2008;47:275-9.
5. Sato K, Fujii Y, Kakiuchi T, Kasono K, Imamura H, Kondo Y, Mano H, Okabe T, Asano S, Takaku F. Paraneoplastic syndrome of hypercalcemia and leukocytosis caused by squamous carcinoma cells (T3M-1) producing parathyroid hormone-related protein, interleukin 1 alpha, and granulocyte colony-stimulating factor. Cancer Res 1989;49:4740-6.
6. Dukes JW, Tierney LM Jr. Paraneoplastic leukemoid reaction as marker for transitional cell carcinoma recurrence. Urology 2009;73:928.e17-9.
7. Kato N, Yasukawa K, Onozuka T, Kimura K. Paraneoplastic syndromes of leukocytosis, thrombocytosis, and hypercalcemia associated with squamous cell carcinoma. J Dermatol 1999;26:352-8.
8. Ma XT, Yu LW, Fu J. Paraneoplastic syndromes of hypercalcemia and leukocytosis associated with colonic metastases from squamous cell carcinoma of the lung. Int J Colorectal Dis 2008;23:129-30.
9. Er O, Coşkun HŞ, Altınbas M, Akgün H, Çetin M, Eser B, Ünal A. Rapidly relapsing squamous cell carcinoma of the renal pelvis associated with paraneoplastic syndromes of leukocytosis, thrombocytosis and hypercalcemia. Urol Int 2001;67:175-7.