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SHORT COMMUNICATIONS AND CASE REPORTS

Synchronous renal cell carcinoma and multiple myeloma: report of two cases and review of the literature

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Summary

Coexistence of renal cell carcinoma (RCC) and multiple myeloma (MM) is an extremely rare condition. Appearance of synchronous RCC and MM was not reported independently so far. In this brief communication, we report 2 cases of synchronous RCC and MM, discuss common risk factors or pathogenetic mechanisms seen in either RCC or MM, point out the importance of IL-6 in this coexistence and provide some descriptive properties of all reported synchronous RCC and MM cases.

Key words: diagnosis, multiple myeloma, multiple primary neoplasms, renal cell carcinoma, second primary neoplasms

Introduction

As knowledge about cancer, its etiology, pathogenesis, and potential treatment increases, clarification of uncommon oncological issues will be possible. Warren and Gates have pioneered the concept of "multiple primary malignancies". They define this situation if a patient has 2 distinct tumors where the possibility of one being a metastasis of the other has been excluded [1]. Coexistence of RCC and MM is an extremely rare condition [2-7]. In previous reports synchronous tumors were not reported independently. Therefore, in the present study, we present 2 patients who had a rarely encountered coexistence of two synchronous cancers, RCC and MM.

Case presentations

Case 1

A 60-year-old male was admitted to the hospital complaining of progressive backache unresponsive to simple analgesics. His past medical history was unremarkable, and he was not under any medications. He did not smoke or drink alcohol. In his family history, one of his brothers had multiple myeloma and one died of colon cancer.

X-ray of the vertebral column revealed a compression fracture of the body of the 12th thoracic (T) vertebra, and multiple millimeter-sized radiolucent lesions of the pelvis. On abdominopelvic computerized tomography (CT), a bulging mass 6×6×5 cm in diameter was seen at the inferior portion of the left kidney and multiple lytic bone metastases were detected in the lumbar (L) vertebrae, sacrum and bilaterally in the iliac bones. A radionuclide bone scan revealed increased osteoblastic activity in the body of the 12th thoracic vertebra, in several ribs and in the pelvic bones.

The lab results showed ESR: 89 mm/h (normal 0-20), BUN: 15.35 mmol/L (normal 2.9-7.1), creatinine: 203 mmol/L (normal 50-100), Ca: 2.42 mmol/L (normal 2.1-2.6), P: 1.19 mmol/L (normal 0.8-1.45), uric acid: 0.54 mmol/L (normal 0.14-0.44), ALP: 132 U/L (normal < 129), PSA: 4.02 ng/ml (normal 0.1-4.0). The rest of the biochemical analyses and complete blood count were within normal range.

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The patient underwent a radical nephrectomy operation in May 2006 with a preoperative presumed diagnosis of metastatic RCC. An intraoperative bone biopsy was taken from the posterior pelvic bone. The pathological examination of the nephrectomy material was reported as follows: RCC, clear cell type, tumor localized within the renal capsule, no invasion of the renal vein or sinus was detected. The bone marrow biopsy revealed 70% plasma cell neoplasia (kappa monoclonal). Serum protein electrophoresis and immunoelectrophoresis showed no abnormality. His serum beta-2 microglobulin was 5.14 mg/L (range 0-2.4), urine immunoelectrophoresis showed kappa and lambda concentrations at 39 mg/dl (normal < 1.5 mg/dl) and < 0.41 mg/dl (normal < 1.5 mg/dl) respectively, with an increased kappa to lambda ratio.

The patient was given palliative spinal radiotherapy between the T^{7th} and L^{2nd} vertebrae, and an appropriate dose of biphoshonate therapy was scheduled.

The patient was accepted as cured concerning his RCC and no further adjuvant therapy was given. However, 5 cycles of VAD (vincristine-adriamycin-dexamethasone) chemotherapy were administered between July –November 2006. After his disease was accepted as being under control (plasma cell in bone marrow biopsy < 5%, urine kappa protein level 0.9 mg/dl) with VAD, in November 2006, thalidomide 200 mg/day + dexamethasone + warfarin treatment was started. The patient is still in remission in terms of his myeloma and RCC, as of March 2008.

Case 2

A 57-year-old male was admitted to the hospital complaining of a pain localized on the right pelvic region in November 2006. He had hypertension for 10 years and was using losartan 50 mg/day. He never smoked or drank alcohol. His mother had died of gastric cancer and his brother died of pancreatic cancer.

On plain radiography of the pelvis, a mass on the right iliac wing was seen. A mass on the right kidney measuring about 3×2 cm in diameter and lesions consistent with bone metastases were seen on an abdominopelvic magnetic resonance imaging (MRI). The radiology report of the lesion of the right kidney was consistent with RCC. An iliac bone marrow biopsy, done for pathological diagnosis, revealed plasma cell neoplasia with 85% plasma cell infiltration (kappa monoclonal). Monoclonal serum proteins were within normal range but urine immunoelectrophoresis showed increased kappa monoclonal protein excretion (47 mg/dl, normal < 1.5).

During the period of investigations acute renal failure developed (BUN 44.28 mmol/L, creatinine 883 mmol/L) and the patient became hemodialysis-dependent. Unfortunately, the patient, who had a pathologically diagnosed plasma cell neoplasia and radiologically diagnosed RCC, was thought by the urologists to be unsuitable for radical nephrectomy. The patient refused a biopsy from the renal mass. After being informed about his cancers, he and his family accepted chemotherapy for the myeloma, which was also considered as determining the short term prognosis of the patient rather than the RCC. Thus, a nephrectomy was planned to be done after VAD chemotherapy. The patient refused to continue chemotherapy after 4 cycles of VAD given until April 2007. On repeat abdominopelvic MRI, the diameter of the mass of the right kidney was stable despite a well-recognized hematological response to chemotherapy (bone marrow plasma cells 10%, urine kappa protein level 2.3 mg/dl). This finding excluded the probability of the renal mass being a plasmacytoma. The patient died of gram-positive bacterial sepsis in August 2007.

Discussion

RCC which originates from the renal cortex constitutes most of the primary renal neoplasms. The incidence of RCC is increasing according to SEER statistics from 1974 to 2004. It has been speculated that this was due to the availability of noninvasive diagnostic tools. Approximately 51,000 new cases of kidney and renal pelvis tumors are expected to be seen in 2007 in the USA, and these constitute 4% of all the estimated new cancer cases [8].

MM, an incurable disease at present, is characterized by the proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. The annual incidence of MM is thought to be stable around 5.5/100,000 in all races over the years. About 20,000 of new cases of MM are expected to be seen in 2007 in the USA [8].

Currently there are no available data concerning differences between the incidence of either RCC or MM in Turkey and in the USA. The age-adjusted incidence of kidney-renal pelvis cancer and MM is 55.5/100,000 and 17.2/100,000 respectively, for a 60-year-old male according to 2000-2004 SEER data [8]. Thus the probability of the coexistence of RCC and MM is roughly one in 10 million for a 60-year-old male.

After a comprehensive literature review, we were unable to find any documented common risk factors, common pathogenetic mechanisms or chromosomal abnormalities seen in either RCC or MM. Smoking,

occupational exposure to toxic compounds, obesity, acquired cystic disease of the kidney, analgesic abuse nephropathy, polycystic kidney disease and genetic factors are well known risk factors for the development of RCC. RCC is also seen together with Von Hippel-Lindau disease and some other hereditary conditions.

The cause of MM is largely unknown. Exposure to ionizing radiation is the strongest single factor linked to an increased risk of MM. Alcohol or tobacco consumption has not been clearly linked to MM. Although direct genetic linkage has not been established, hereditary or genetic factors may predispose to MM development. For our patients, their family cancer histories in first-degree relatives makes us consider a familial predisposition to cancer as a probable etiology.

IL-6, originally identified as a B-cell differentiation factor, causes proliferation of plasmoblastic cells and induces terminal differentiation of B cells into antibody-producing cells. There is evidence that some myeloma cells produce IL-6 and also that some express high levels of IL-6 receptors. Suppression of myeloma cell proliferation by anti-IL-6 antibodies has been shown. IL-6 is also produced by some RCC cell lines *in vitro*. IL-6 has been detected in the serum of patients with advanced RCC. Experimental evidence has shown that IL-6 can act as an autocrine growth factor in human RCC [9]. These observations suggest that IL-6, possibly released from RCC cells, could contribute to the development or progression of MM. Sakai et al. reported a 67-year-old male having synchronous RCC and MM. The patient's initial serum levels of IL-6 decreased after nephrectomy. It was shown that the RCC cells had IL-6 activity, and proliferation of the cultured myeloma cells was stimulated by IL-6 *in vitro* [2]. It would have been a valuable contribution if we had measured serial serum IL-6 levels before and after treatments in our patients. Whether the presence of one malignancy triggers and feeds another one is a question to be answered not only for the coexistence of RCC and MM but also for all synchronous tumors.

Coexistence of RCC and MM is a rarely seen condition. To our knowledge, the presented patients are the 5th and 6th cases having both synchronous RCC and MM (Table 1). Notably, there is a tendency of RCC to precede MM in most of the reported metachronous cases (10 of 14 cases, 71%) [3-5,7]. Also men are affected more than women as 11 of 14 (78%) metachronous cases were male. According to SEER statistics, the age-adjusted incidence of RCC for men is twice that of women [8], therefore what makes men more prone to have coexistent RCC and MM is a mystery for the present. We hope that acumulating data from case series, retrospective database reviews and prospective immunological/genetic studies will throw light on these questions.

Table 1. Summary of the cases having synchronous RCC and MM reported so far in English literature

Authors [Reference]	*Case no./ Gender*	*Age (yrs) at diagnosis*	*Appearance of tumors*
Law and Blom [6]	1 / M	67	Synchronous*
Sakai et al. [2]	2 / F	67	Synchronous
Choueiri et al. [7]	3 / M	47	Synchronous
Choueiri et al. [7]	4 / M	66	Synchronous
Present case #1	5 / M	60	Synchronous
Present case #2	6 / M	57	Synchronous

*Tumors accepted as "synchronous" when the time interval between diagnosis of two different primary cancers was ≤ 3 months; F: female, M: male

Although in both RCC and MM case series a tendency to second malignancies has been reported [3,6,7,10], there is a limited number of papers reporting a coexistence of both tumors. In the light of these reports, currently, a strong belief has arisen that this coexistence can not be explained by chance alone. Up to now, 6 patients including ours with synchronous RCC and MM have been reported. Various factors have been discussed attempting to find a common etiopathogenetic explanation such as genetic alterations, environmental factors or a common immune-mediated process. In our cases, a familial tendency to carcinogenesis (whether dependent on exposure to an unidentified environmental insult or on a genetic alteration) may be considered as a probable cause. Besides this, it has been shown that RCC cells feed myeloma cells immunologically via IL-6, suggesting that, in a suitable genetic milieu, the occurrence of one tumor may trigger another one. Whether the presence of RCC (especially the ones that express high IL-6) provokes MM development is a question that we are unable to answer at present. In fact this needs to be answered not only for RCC and MM coexistence but also for all multiple synchronous tumors. In conclusion, multiple primary malignancies are not uncommon today. Further investigations concerning a common etiology, common probable genetic alterations and interactions of these tumors need to be carried out.

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