Annals of Medicine and Surgery 27 (2018) 9–16

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Review

Skeletal metastasis in renal cell carcinoma: A review

Masood Umer, Yasir Mohib*, Muhammed Atif, Muhammad Nazim

Aga Khan University Hospital Karachi, Pakistan

ARTICLE INFO

Keywords:
Renal cell carcinoma
Nephrectomy
Pathological fracture
Impending fracture
Metastasis

ABSTRACT

Background: Renal cell carcinoma account for 3% of all cancers, with peak incidence between 60 and 70 years of age predominantly affecting male population. Renal carcinoma is the most common malignancy of kidney constitutes for 80–90% of renal neoplasm with an overall 45% five years survival rate. Majority are diagnosed incidentally during investigation for other disease process of abdomen. Classical triad of gross hematuria, pain and palpable mass in abdomen is rare accounting to only 6–10%. Treatment of early stages of disease i.e. localized disease is partial or radical nephrectomy. Most common metastasis in RCC occurs to lung, followed by bone involvement in 20–35%, lymph nodes, liver, adrenal gland and brain. In metastatic disease median survival rate of patient is about eight months with 50% mortality rate within first year of life, five years survival rate is 10%. Skeletal metastasis are very destructive in patients with renal cell carcinoma compromising bone integrity leading to skeletal related events including pains, impending fractures, nerve compressions, hypercalcemia and even pathological fractures which may require surgical interventions and other therapy. In addition to skeletal complications, presence of bone metastases in RCC has negative impact on progression free survival and overall survival of patients treated with systemic therapies.

Objective: In this review we discuss pathophysiology of tumor metastasis, diagnosis, management and Case examples of metastatic renal cell carcinoma.

Conclusion: Incidence of metastatic renal carcinoma is increasing. Overall prognosis of patient with advanced RCC is poor, emphasizing the importance of early detection and prompt treatment of primary lesion in its early stage. Advancement in targeted therapy in recent decades had made some improvement in treatment of SREs and has helped in improving patent's quality of life but still we are in need of further improvement in treatment modalities to cure disease thereby decreasing morbidity and mortality.

1. Introduction

Renal cell carcinoma account for 3% of all cancers and commonly occurs in western countries [1]. Its peak incidence found between 60 and 70 years of age and is more common in men than women. Renal carcinoma is the most common malignancy of kidney constitutes for 80–90% of renal neoplasm with an overall 45% five years survival rate. Renal cell carcinoma [RCC] is subdivided into clear cell, papillary and chromophobe but clear cell variety is the most common. Due to increased use of modern diagnostic modalities of choice like ultrasound and CT scan, diagnosis of RCCs has increased in early stages [2] and majority are diagnosed incidentally during investigation for other disease process of abdomen [4]. Classical triad of gross hematuria, pain and palpable mass in abdomen is rare accounting to only 6–10% [3]. Ultrasound and cross sectional imaging like CT scan and MRI are needed to establish diagnosis. Treatment of early stages of disease i.e. localized disease is partial or radical nephrectomy. Recurrent lesion [> 10 years] is rare in RCC [4]. The recurrence rate are about 10.5%–21.6% at 15 and 20 years respectively as described by Miyao et al. [5].

Most common metastasis in RCC occurs to lung, followed by bone involvement in 20–35% [6], lymph nodes, liver, adrenal gland and brain. In metastatic disease median survival rate of patient is about eight months [7] with 50% mortality rate within first year of life, five years survival rate is 10% [8].

Skeletal metastasis is very destructive in patients with renal cell carcinoma leading to mainly osteolytic lesions that compromise bone integrity and negatively impact patients outcome. Skeletal involvement in RCC is associated with skeletal related events [SRE] including pains, impending fractures, nerve compressions, hypercalcemia and even pathological fractures which may require surgical interventions and other therapy [9, 10]. Swanson et al. studied 947 patients with renal cell carcinoma and skeletal metastasis was found in 26.7% of patients which mostly involved spine, pelvis and proximal femur [11]. In

* Corresponding author.
E-mail addresses: masood.umer@aku.edu (M. Umer), Yasir.mohib@aku.edu (Y. Mohib), muhammad.nazim@aku.edu (M. Nazim).

https://doi.org/10.1016/j.amsu.2018.01.002
Received 9 October 2017; Accepted 14 January 2018

addition to skeletal complications, presence of bone metastases in RCC has negative impact on progression free survival and overall survival of patients treated with systemic therapies.

Santoni et al. investigated patients with bone metastases from RCC and found patients' age, ECOG performance status, histology, MSKCC prognostic score, presence of concomitant metastasis and time from nephrectomy to bone metastases [TTBM] to be significant factors associated with prognosis [12].

Kume et al. analyzed 94 patients with mRCC to bone and on a multivariate analysis found that sarcomatoid differentiation of RCC, vertebral bone involvement, extra-osseous metastases, alkaline phosphatase > 1.5 times normal and C-reactive protein > 0.3 mg/dl were significant risk factors that adversely effect overall survival [13].

2. Pathophysiology of tumor metastasis

Skeletal metastatic lesions are divided into three types: Osteolytic, osteoblastic and mixed. Activity of osteoclasts is responsible for osteolytic lesion and their activating mechanism varies according to different types of primary malignancies. Osteoclasts are derived from hematopoietic stem cells [monocyte-macrophage lineage] and mainly they resorb mineralized bone matrix by creating microenvironment and ultimately undergo apoptosis. In normal metabolism, bone micro-environment enhances osteoclast production by forming different molecules like macrophage colony stimulating factors and receptor activator of nuclear factor kB [RANK] and its ligand [RANKL] by stromal cells, osteoblast, activated T-cells, tumor cells and osteoclast precursor cells. Bone metastases develop by occupation of bone erythropoietic system by cancer cells. Interaction of tumor cells and bone micro-environment induces immune cells to release factors that attract and stimulate osteoclasts thereby causing increased bone turnover and destruction [9].

The discovery and characterization of the essential cytokines for osteoclast biology, receptor activator of nuclear factor [NF]-kB ligand [RANKL], its receptor RANK, and its decoy receptor osteoprotegerin [OPG] have led to a concept of bone metabolism. With accumulating evidence of the role of the OPG/RANKL/RANK system in normal skeletal physiology, it became clear that many clinically relevant metabolic bone diseases in humans, including inflammatory bone diseases e.g., rheumatoid arthritis, malignant bone tumors e.g., myeloma or osteolytic metastases and different forms of osteoporosis are related to, or caused by, alterations of the OPG/RANKL/RANK system [9].

3. Bone cells and immune system

A complex system of interaction exists between bone and body immune system at molecular level. This includes RANK, RANKL and natural decoy receptor osteoprotegerin [OPG]. Higher serum ratio of RANKL/OPG promotes osteoclastogensis [14]. Mikami at el [15]. stated that expression of RANKL and RANK is directly related to stage of primary lesion and metastasis to bone and other organ.

4. Bone cells and renal cell carcinoma

The pathogenesis of skeletal metastasis in RCC is same as for breast cancer. A vicious cycle exists between tumor cells and bone. Osteoclast activation due to presence of malignant cells lead to bone destruction with secretion of different bone-derived growth factors and cytokines which facilitate cancer cell proliferation and enhance tumor growth. These include transforming growth factor-beta [TGF-β], fibroblast growth factors [FGF], insulin like growth factors and bone morphogenic protein and many more. These factors not only stimulate the local growth of RCC cells but also circulate and stimulate remote metastatic growth [16]. Tumor cells are responsible for release of prostaglandins, activated vitamin D, tumor necrosis factor [TNF], para-thyroid hormone and its related peptide, these activates osteoblast and stromal cells on bone marrow by interacting through RANKL system and ultimately stimulates osteoclast activity.

5. Osseus metastasis in RCC and role of different molecular mediators

Bone is a source of numerous growth factors, thus enabling survival of metastatic tumor cells. Kominsky et al. [17] studied that RCC bone metastasis cells can be stimulated by transforming growth factor-beta1 [TGF-1] in vivo. This interaction increases tumor growth and bone destruction. They also concluded that inhibition of TGF-1 helpful in treatment of RCC bone metastasis.

Weber et al. [18] demonstrated that growth factor signaling pathway which includes epidermal growth factor receptors [EGF-R] and transforming growth factor beta receptor [TGF-betaR] play a vital role in RCC- activated osteoclast bone resorption and inhibition of this signaling pathway decreases RCC bone metastasis.

Joeckel et al. [19] demonstrated a positive relationship between extracellular calcium concentration and RCC with the help of calcium sensing receptor [CaSR]. Higher expression was found in RCC and calcium treatment leads to increase RCC proliferation.

PTHrP is a polypeptide and is released by normal as well as malignant cells, regulating growth, differentiation and death. Massfelder et al. [20] studied that blocking of PTHrP with antibodies or antagonizing PTHrP receptors increases cell death in RCC. Talon et al. [21] demonstrated blocking PTHrP system can be employed for therapeutic treatment of RCC in clinical setting.

There are many more molecules which involves in regulation of renal cell carcinoma, immune system and skeletal metastasis. These include isuline mRNA binding protein-3 [IMP3][22], caderrin-11 [23], AKT/integrin-5 signaling system [24], MicroRNAs [miRNAs] [25] and matritase [26]. Studies are still needed for better understanding of more signaling pathways to improve prognosis of RCC.

6. Diagnosis of RCC skeletal metastasis

Early diagnosis and prompt treatment reduces long term skeletal complications [6]. Like other malignancies, bone scan is the imaging modality of choice to determine metastatic bone growth for patient with RCC. Plain radiograph shows pure lytic lesion and helpful to identify impending or established fracture.

Bone scan shows osteoblastic activity in the form of hot spots [27]. In osteolytic lesion, compensatory osteoblastic activities increase, hence producing hotspots even in lytic lesion. Therefore early lesions in RCC have difficulty in detection by bone scan. Patient may present with hyper-calcaemia, spinal cord or nerve root compression, pain with impending fracture or pathologic fracture. Non-symptomatic patients produce few positive results. Hence bone scintigraphy is more helpful in symptomatic patients.

Positron emission tomography [PET] and whole body MRI are also used for diagnosis of lesion. It can quantify lesion and is helpful for monitoring during followup. Some studies may describe that PET may replace bone scanning but it is expensive [28].

MRI is the investigation of choice in lesion with cord compression. Studies have proved superiority of MRI over PET in detecting renal bone metastasis besides non-requirement of any labeling agent [radiopharmaceutical Drug].

7. Management

Metastatic lesions are commonly encountered with local pain, spinal cord compression/deficit, fracture and hypercalcaemiaof malignancy. Goal of treatment includes prevention of theses complication, pain palliation and improvement in quality of life [29]. Management of lesion involves adequate history and physical examination and metastatic workup. Multidisciplinary approach should de needed, comprising of orthopedic surgeon, urologist, radiologist, pathologist, radiation