CASE REPORT
HEMATOLOGY

Diseases & Research

Primary Extramedullary Plasmacytoma of the Kidney: A Case Report and Literature Review

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Abstract: Extramedullary plasmacytomas (EMPs) usually occur in the upper respiratory tract, the occurrence in the kidney is extremely rare. The present study reported a case of primary renal plasmacytoma in a 46-year-old male patient with frequent and urgent urination, nocturia increased due to renal failure. Computed tomography (CT) imaging showed a 60×58 mm enhanced mass at the lower pole of the right kidney. Following the radical nephrectomy, histopathological and immunohistochemistry analysis of the resected specimen supported the diagnosis of plasmacytoma. Bone marrow biopsy and total body skeletal survey was performed to demonstrate that there were no evidence of multiple myeloma (MM) and bone lesions. Consequently, a diagnosis of a primary renal EMP was proposed. Subsequently, the patient was treated with 4 course of chemotherapy VAD (vincristine, epirubicin and dexamethasone) + cyclophosphamide + thalidomide, and he was disease-free during 4 years' follow-up time. The current study also presents a review of the literatures. Treatment of primary renal EMP is surgery, radiotherapy, chemotherapy or a combination of those, even hematopoietic stem cell transplantation may be also an option. Long-term follow-up is a necessity for systemic control due to the possibility to transform into MM.

Keywords: Plasmacytoma; Myeloma; Kidney; Therapy.

Introduction

Extramedullary plasmacytoma (EMP) is a rare malignant neoplasm that develops due to uncontrolled plasma cell proliferation and monoclonal plasmacytic infiltration[1]. EMP typically affects patients at their middle ages, and is more common for male. Risk factors of plasmacytomas still remain unconfirmed. However, prior radiation exposure has been suggested[2]. Isolated primary EMP occurs more commonly in the nasopharynx, larynx and upper respiratory tract, whereas EMP due to hematogenous spread of multiple myeloma (MM) mainly occurs in gastrointestinal tract, pleura, testis, skin, peritoneum, liver, endocrine glands and lymph nodes[3]. EMPs retroperitoneal infiiltration, especially primary renal plasmacytoma is very rare. Herein we report a rare case of primary renal EMP with direct parenchymal invasion of the kidney causing renal failure.

Case Presentation

A 46-year-old man was admitted to our hospital in December 9, 2011. He already had 1-year history of increasing facial, blepharal and pretibial edema, frequent and urgent urination, and increasing nocturia, but he did not have odynuria, dysuria, hematuria, loin pain, hydrothorax, ascites, anorexia, weight loss, or stone disease. His past medical history was unremarkable. Physical examination revealed no swollen lymph nodes. His both renal regions were sensitive to percussion, and his neurologic deficit was non-evi-dent.

Laboratory tests at admission were as follows: blood cell counts were normal; serum creatinine was raised significantly; C-reactive protein and erythrocyte sedimentation rate were also elevated; test for Bence-Jones protein was negative; serum and urine electrophoresis for paraproteins were normal. Enhanced computed tomography (CT) imaging showed a 60×58 mm en-hanced mass at the lower pole of the right kidney, without any swollen lymph nodes (Fig. 1). Then the radical nephrectomy was performed, which showed that the renal interstitial cells were infiltrated by plasma cells diffusedly with the expression of im-munoglobulin (Ig) kappa highly but Ig lambda partly (Fig. 2), the renal tubules were atrophy seriously. Neoplastic cells were pos-itive for CD38 (Fig. 3) and negative for CD45 and CD20. Bone marrow biopsy was normal. Then a whole body skeletal survey was performed, which didn't reveal any lytic bone lesions. All these observations were consistent with a diagnosis of a primary renal EMP.

Following the multidisciplinary team discussion, as renal failure due to the plasmacytoma, the further initial management was chemotherapy and renal support therapy. The procedure was challenging due to no standard chemotherapy for EMP. Then a traditional chemotherapy regimen of MM, VAD (vincristine, epirubicin and dexamethasone) + cyclophosphamide + thalidomide was chosen to treat him. After 4 cycles of chemotherapy, his renal function recovered, and he was in good health without any

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clini-cal evidence of neoplasia in other sites or hematological disease. Then the patient was regularly followed up in the outpatient de-partment for 1~3 months. No obvious abnormalities were found in abdominal B-scan ultrasonography, blood and urine immuno-fixation electrophoresis, Bence-Jones proteins test, etc. By 2016-02-28, he had and still kept disease-free for over 4 years.

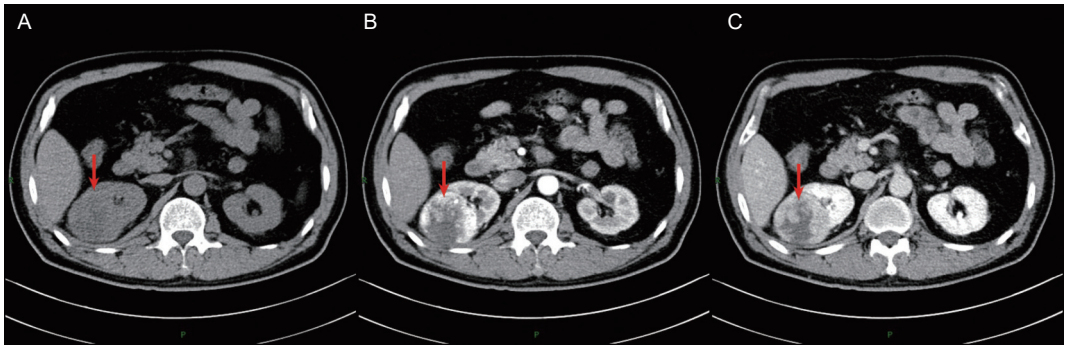

Fig. 1. Imaging examination of the patient.
The abdominal enhanced computed tomography(CT) imaging showed that an enhancing mass at the lower pole of the right kidney measuring 60×58 mm, without any swollen lymph nodes. (A) plain scan, (B) arterial phase, (C) venous phase.

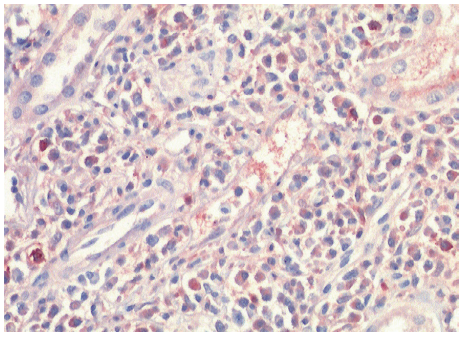

Fig. 2. Histopathological examination showing renal interstitial cell was infiltrated by plasma cell diffusedly with the expression of Ig kappa highly (H&E × 200).

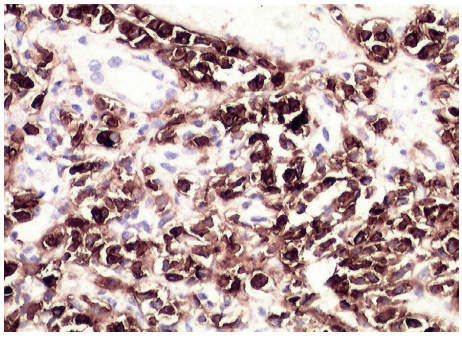

Fig. 3. High power view (H&E × 200) showing neoplastic cells were positive for CD38.

Primary renal EMP is rare, here we summarized its clinical characteristics and treatment according to our experiences and relevant literatures by 2016, as follows:

Clinical presentation

Primary renal EMPs often have no typical clinical manifestation. They may be found by physical examination, even presented by the symptom of obstruction, pain or bleeding, which depended on the mass's volume and the site of involvement. Only some rare case have the symptoms of extramedullary hematopoiesis[4]. Our patient presented increasing facial, blepharal, pretibial edema due to renal injure and was found a mass in the right kidney. Direct renal failure may be a common lesion due to plasma cell dyscrasias. The detailed mechanisms of kidney injury in plasma cell malignancies include cast nephropathy, amyloid light-chain amyloidosis, monoclonal Ig deposition disease, glomerulonephritis, hyperviscosity syndrome, hypercalcemia, tumor lysis syndrome, tubulointerstitial nephritis, and direct parenchymal invasion by plasma cells[5].

Imaging examination

CT and magnetic resonance imaging (MRI) are complementary techniques in evaluating the size and location of the renal EMP and the involvement of the adjacent structures. The CT features were described as heterogeneously enhancing mass, tumor or nodule, which can be well enhanced with peripheral or with gradual filling towards the center of the lesion, some even show the secondary changes occasionally with hemorrhage necrosis and punctate calcification[6]. On MR images, most renal EMP were displayed as tumor with intermediate or slightly higher signal intensity on the T1- weighted, moderate-to-high signal intensity on the T2-weighted images and heterogeneous enhancement on the contrast-enhanced MRI[7]. Although MRI was superior to CT in identifying the malignant characters of the soft tissue mass, it could not distinguish plasmacytoma from other probable causes, such as squamous cell and adenocystic carcinoma. 18F-fluorodeoxyglucose (18F-FDG) is a successful avid agent for diagnosis and monitoring of disease status in plasmacytoma, so the ability to perform the whole-body examinations that enable sensitive detection of intramedullary and extramedullary lesions in one session is a major advantage of fluorodeoxyglucose positron emission tomography computer tomography (FDG PET/CT) over MRI[8]. Furthermore, 18F-FDG PET/CT has been found to be useful in staging, identifying optimal sites for biopsy, restaging, and monitoring response to treatment for MM and related plasma cell dyscrasias[9]. Nevertheless, 18F-FDG uptake is also common in benign entities such as physiological uptake and the use of 18F-FDG PET/CT in EMPs is limited in the literature owing to the

small number of cases. Overall, the imageology appearance of renal EMPs are very limited distinctly.

Pathological and immunohistochemical findings

The primary EMP of the kidney showed the plasma cells was often extended and infiltrated to the renal capsule even perirenal adipose tissue. In histology, the plasma cell is nodular lesions isolatedly with no obvious boundaries to surrounding tissue, and in microscope, it is distributed diffusely with mature, inmature or anaplastic plasma cells. Immunophenotyping with CD38 (+), CD138 (+), IgA, IgD, IgG, IgM, IgE, kappa light chain, and lambda light chain antibody are helpful to differentiate EMPs from other tumors, and AE1/AE3(-) can distinguish between with epithelial tumors[10].

Diagnosis

To the best of our knowledge, the primary renal EMP is lack in the evidence of typical clinical symptoms and specific laboratory tests, so the diagnosis may be difficult. In clinic, once the neoplasm is found in the kidney and be confirmed to be infiltrated by plasma cell, the diagnostic criteria of primary renal EMPs were as follows: 1) neoplasm confined to the primary site, with or without lymphonodus' lesion; 2) serum and urine protein electrophoresis, immunoelectrophoresis, urine Bence Jones proteins were probably negative, but there were no other lesions, also no evidence of systemic signs and symptoms associated with MM or other soft tissues plasmacytoma through general systematic physical examination including the bone marrow biopsy and radiological examination. So the diagnosis of primary renal EMP can be made only after detailed clinical, hematological, biochemical, radiological, molecular-pathologic and immunohistochemical investigations excluding the possibility of localized presentation of MM such as in our case[11].

Treatment

Talking about the treatment of the EMP, controversy exists in the optimal treatment of EMP, but the current reported experiences of treating primary EMPs indicate that surgery, radiotherapy, chemotherapy or a combination of those are the optional choice. As primary renal EMP always showed an isolated mass, so initial management was surgical with radical nephrectomy of the lesion kidney, but partial nephrectomy was also reported. Furthermore, plasmacytomas are generally very radiosensitive, so radiation therapy is also a therapeutic modality for EMP. Certain studies re-ported that local radiotherapy might achieve excellent local con-trol[12], but no does-response relationship was observed now. The optimal radiation should be considered if feasible. However, there is no recommendation for adjuvant radiotherapy to patients who have undergone complete surgical excision with negative margins[13].

Chemotherapy is advisable for patients who have a generalized EMP, refractory or relapsed disease. But efficacy of chemother-apy is poorly studied and based mostly on case reports or small retrospective studies of patients. Regimens used for MM can be considered. Furthermore, thalidomide combined with dexameth-asone or alkylating agents were used to be effective and increase the response rate[14]. Thalidomide had been reported to have not only an antiangiogenic effect, but also to act a role directly on myeloma cells[15], so from this perspective, thalidomide could be expected to have some effect on extramedullary masses. In 2013, Sekiguchi Y, et al[16] had summarized 27 cases of EMP who were treated with thalidomide from 2005 to 2011, they reported that thalidomide was effective but it's duration of effect was relatively short and immature myeloma might be resistant to thalidomide. González -Porras et al[17] reported that thalidomide in combina-tion with cyclophosphamide and dexamethasone was effective in soft-tissue plasmacetomas. In the present study, patients who received regimens containing novel drugs, such as bortezomib, tended to have better responses[18]. Other chemotherapy regimens need to be further developed.

As is known to us, autologus and allogeneic hematopoietic stem cell transplantation (HSCT) have been widely used to the patients with MM, however, the use of HSCT in the management of EMP were restricted to few reports. The role of HSCT in the management of EMPs was not defined. But it was reported that autologous HSCT could be able to achieve responses in extramedullary sites even in patients who had no response to chemotherapy despite a serologic response[14]. And high-risk plasmacytoma pa-tients with deletion of chromosome, plasma blastic morphology, high LDH with extramedullary disease such as plasmacytoma in central nervous system should have allogeneic HSCT as con-solidation early in the course of the disease to achieve maximal survival benefiits[14]. But there is a paucity of prospective data from HSCT randomized trials, especially in primary renal EMPs. Unquestionably, more experience is needed to study the effect of HSCT in EMPs in general.

Prognosis

Compared to solitary bone plasmacytoma, EMP demonstrates a relatively low risk of progression to MM. The survival at 10 years of EMP is 70%[13], and the rate of progression to MM is lower than in solitary bone plasmacytoma, ranging from 11~30% at ten years[19]. The primary renal EMP's prognosis is different in the literatures. Radiotherapy and serum β2 microglobulin<3.5 mg/L were found to be favorable prognostic factors for EMP patients[20]. A higher failure rate in 'high grade' tumours using the MM grad-ing criteria and reminded that tumours >5 cm were at higher risk of failure[13].

Literature review

An internet PubMed search was performed for the literature review with the key words "extramedullary plasmacytoma, kidney, retroperitoneal, renal". A total of 18 patients of primary renal EMP were reported in the English literature from 1990 to 2016 (Table 1)[2, 4, 6, 11, 21–34]. In our review, primary renal EMP occurred mainly in adult with ages from 28 years to 83 years, the male/ female ratio of which was 13:5. Common clinical features of the reviewed patients include pains in back, lumbar or abdomen, sometimes with hematuria, edema, abdominal distention, etc. However, 6 of them did not have these common symptoms and were diagnosed by ultrasonography or CT scanning. Swollen masses were found by CT scanning or ultrasonography in kidneys of all the patients, but at different locations: in the left kidney of 12 patients, in the right kidney of 5 patients, and in the al-

Table 1. The detailed clinical features of the 18 primary renal EMPs reported in English literatures from 1990 to 2016.

Authors[Ref]	Age (years)/ gender	Presentation	Location	SPE	Bence-Jones protein	Treatment			Prognosis
						Surgery	Chemotherapy	Radiotherapy	
Spence RA, et al[2]	49/M	loin pain	R	N	-	RN	NO	NO	NA
Mimura R, et al[4]	62/M	extremities with paresthesia	L	IgG κ ↑	NA	RN	NO	NO	NA
Monill J, et al[6]	43/M	NA	L	IgG κ ↑	-	NA	NA	NA	NA
Mongha R, et al[11]	58/M	right lumbar pain	R	N	-	RN	NO	YES	alive after 1 year
Igel TC, et al[21]	64/M	asymptomatic	L	IgM κ ↑	-	RN	NO	YES	alive after 16 years
Kanoh T, et al[22]	76/F	hematuria, abdominal distention, back pain	L	NA	-	RN	NO	NO	died after 2 months
Kobayashi H, et al[23]	83/M	abdominal pain and palpable mass	L	N	-	RN	NO	NO	died 10 days postoperatively
Shustik C, et al[24]	31/M	asymptomatic	NA	IgG κ↑	NA	RN	NO	NO	alive after 33 months
Chen TC, et al[25]	28/M	abdominal pain, jaundice, tea-colored urine and clay stool	R	IgG κ ↑	+	NO	YES	YES	alive after 1 year
Park SY, et al[26]	39/M	asymptomatic	L	N	NA	RN	YES	YES	died after 34 months
Yazici S, et al[27]	67/F	asymptomatic	L	κ ↑	NA	RN	NO	NO	alive after 6 months
Yang GF, et al[28]	76/F	back pain	L	N	NA	RN	NO	NO	NA
Klein T, et al[29]	82/F	Hematuria, hydronephrosis	R	NA	NA	RN	NO	NO	NA
Zhong Y, et al[30]	41/M	epigastric discomfort	L	NA	-	RN	NO	NO	NA
Ozkok A, et al[31]	68/M	edema, dyspnea, and low urinary output	L	N	-	NO	YES	YES	died after 14 years
Zhang SQ, et al[32]	46/F	asymptomatic	L	NA	+	PN	NO	NO	alive after 9 months
Berquist SW, et al[33]	51/M	hematuria	L	IgG↑	NA	PN	NO	NO	alive after 28 months
Hu G, et al[34]	70/M	asymptomatic	R	NA	NA	PN	NA	NA	NA

EMP, extramedullary plasmacytoma; F, female; M, male; L, left kidney; R, right kidney; NA, not available; N, normal; SPE, serum protein electrophoresis; Ig, immunoglobulin; ↑, increased; +, positive; -, negative; PCN, plasma cell neoplasm; RN, radical nephrectomy; PN, partial nephrectomy.

lograft of 1 kidney transplant patient. For the therapy, 12 patients under-went radical nephrectomy of the lesion kidney, 3 patients received partial nephrectomy. However, only 3 patients received adjuvant chemotherapy, and only 5 patients were treated with adjuvant ra-diation therapy. Chemotherapy regimens were vincristine, doxo-rubicin, dexamethasone, and thalidomide, etc. Prognosis varied in different literatures, with survial time range from 10 days to 16 years (Detailed informations were seen in Table 1).

Discussion

Plasmacytoma is a clonal plasma cell malignancy, its cells usually reside in the medullary cavity of bone marrow, but when spreading to the cortical bones, or spreading hematogenously to other organs, they may cause extramedullary diseases[14]. In practical terms, isolated primary plasmacytoma is compounded with solitary bone plasmacytoma and extraosseous plasmacyto-ma. Solitary bone plasmacytoma just means plasma cell myeloma come from the bone cortex without evidence of any other lesion, while extraosseous plasmacytoma so called EMP was defined by the updated WHO classification (2008) as localized plasma cell neoplasm that arised in soft tissues other than bone[35]. In the Surveillance, Epidemiology and End Results (SEER) Program (1992–2004) of United States, the data displayed that the incidence of bone plasmacytomas was 40% higher than EMPs[36]. EMP is uncommon tumor, with a worldwide annual incidence of 3 per 100, 000 populations, which account for less than 3~10% of all plasma cell neoplasms[37]. It is three times more common in male and the median age is 55 years which is around ten years younger than the patients with MM[11]. It occurs most commonly in the head and neck region, followed by gastrointestinal tract,

central nervous system, thyroid, breast, parotid gland, testis, and lymph nodes[38]. However, retroperitoneal plasmacytoma especially re-nal plasmacytoma is an even rarer entity.

Based on the published literatures, EMP usually develops in the head and neck soft tissues, however, primary renal EMP is a rare clinical entity, presenting diagnostic and therapeutic challenges due to its unusual location and nonspecific or absent symptoms and lack of standard therapy, it is essential to recognize them in the differential diagnosis of primary benign or malignant tumors of the kidney. There is no typical clinical manifestation, but imaging evaluations may state the existence, size and location of the tumor, especially PET-CT. Radiological findings in renal plasmacytoma are indistinguishable from those of renal cell carci-noma but tissue biopsy showing monoclonal plasma cell histolo-gy without any evidence of MM and plasmacytoma of other sites is the only way to diagnosis. A comprehensive search in PubMed database for patients with renal EMPs identified only dozens of reports. However, more cases might have occurred because some cases were underdiagnosed or underreported. A treatment regimen of local surgery, local radiotherapy, chemotherapy or a combination of them may be initiated. Most of these cases had re-ceived surgery such as radical nephrectomy, a few combined with radiotherapy or chemotherapy. In addition that, some of them were deficiency in the outcome and prognosis, but the longest follow-up time was 16 years. As per the case-based experience in the literature, factors that influenced the good prognosis in our case are early presentation, a single site of involvement, local-ization, absence of M protein, and prompt medical attention and treatment. Although the general prognosis and outcome for EMP is good, long- term follow-up in terms of disease recurrence and progression is mandatory.

Abbreviations

CT, computed tomography; EMPs, extramedullary plasmacytomas; FDG PET/CT, fluorodeoxyglucose positron emission tomography computer tomography; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; MM, multiple myeloma; MRI, magnetic resonance imaging; VAD, vincristine, epirubicin and dexamethasone; 18F-FDG, 18F-fluorodeoxyglucose.

Conflict of interest

The author have no conflict of interest to declare.

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