Original paper

Renal tumors in unselected forensic post-mortem material

Ewa Rzepecka-Woźniak[1], Anna Trzepla[1], Krzysztof Okoń[2]

[1]Department of Forensic Medicine, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Pathomorphology, Jagiellonian University Medical College, Krakow, Poland

The frequency of clinically evident renal tumors is increasing, due to an actual increase in incidence, but also due to an improvement in detection methods. The aim of the present study was to analyze the incidence of renal tumors in an unselected autopsy series. A search for renal tumors was conducted based on the autopsy reports from the Department of Forensic Medicine. The slides were reviewed and reclassified according to current criteria. Among 14,904 autopsies, 80 renal tumors were found. The most frequent tumor types were clear cell carcinomas (41%), papillary carcinomas (18%) and cortical adenomas (19%). There were 66 males and 14 females. The average age was 57.83 for males and 62.86 for females. The characteristics of the study group were not exactly identical but similar to other autopsy series, and significantly different from surgical series.

Key words: renal tumors, renal cell carcinoma, incidental renal carcinoma, autopsy, forensic autopsy.

Introduction

Renal cell tumors have gained considerable interest in recent years. This is due to better understanding of their molecular pathogenesis which has resulted in the development of new strategies of treatment, particularly the use of targeted drugs. Worldwide, renal cell carcinoma is on the 14th place among the most frequent cancers (11th in males, 15th in females) [1]. The incidence in developed countries is higher, and it is considered the most deadly urologic malignancy. For the USA, the incidence is 20.7/100 000 in males and 10.5 in females. A 5-year survival rate is 70% [2]. In Poland the incidence is 10.0 in males and 5.4 in females [3]. Interestingly, in most series there is a stepwise increase in incidence, although this trend seems to have reversed in the last few years, at least in some countries. The reasons for the changes in incidence are unclear, as are the etiological factors for renal cell carcinoma; however changing trends in tobacco smoking may be one of the most important factors. Also, the increased incidence is accompanied by considerable stage migration. Indeed it was suggested that the incidence increases primarily in proportion to the detection of small tumors [4-8]. In particular the introduction and wide availability of ultrasonography resulted in a significant increase in renal tumor detection, as well as stage, grade and type migration [8].

Some interesting information about the epidemiology of cancer may be obtained by analyzing post-mortem material. We previously reported incidence of renal tumors in a series of hospital-derived autopsies [4]. The hospital population may however significantly differ from the general population. The forensic medicine departments may provide another source of autopsy material, giving further insight into the epidemiology of renal tumors.

Material and methods

The autopsy reports generated at the Department of Forensic Medicine between 1994 and 2008 were reviewed for the presence of any renal tumors; in such cases the original hematoxyllin and eosin stained

slides as well as paraffin blocks were retrieved and were reviewed by authors using a multiheaded microscope. The autopsy samples of renal tumors were fixed in formalin, routinely processed and paraffin embedded. From the paraffin blocks, 3 μm sections were prepared and stained by hematoxyllin and eosin by standard protocol. All the tumors were reclassified using standard criteria [9]. For dubious cases, the paraffin blocks were retrieved and new slides prepared. If required for the classification, we used immunohistochemistry for pan-cytokeratin, cytokeratin 7, high molecular weight cytokeratin, cytokeratin 19, and epithelial membrane antigen performed by standard protocol; the primary antibodies are listed in the Table I. Briefly, the slides were dewaxed, rehydrated and incubated in 3% peroxide solution for 10 minutes to block endogenous peroxidase activity. Antigen retrieval was carried out by microwaving in citrate buffer (0.2% citric acid titrated to pH 6.0 with 2N NaOH) at 750W for 3 × 5 minutes. Primary antibodies, all manufactured by DAKO, (DAKO, Denmark) are listed in Table I. The LabVision (Thermo Fisher Scientific, USA) detection system was used. 3-amino-9-ethylcarbazole served as the chromogen. The slides were counterstained with Mayer's hematoxylin (DAKO, Denmark).

The statistical analysis was performed with Statistica 10 (StatSoft Inc., USA), using Pearson's χ^2 test, Mann-Whitney U test, Kruskal-Wallis ANOVA when appropriate. The significance level was set to 0.05.

Results

Between 1994 and 2008 a total of 14,904 postmortem examinations were performed at the Department of Forensic Medicine. In this material we found 80 renal tumors, that is equal to 0.54% of the postmortem examinations. The average age of the persons with renal tumors was 58.73 years (range 21 to 86, SD 13.53). There were 66 males and 14 females. The average age for males was 57.83 and 62.86 for females. The difference in age between genders was not statistically significant. The cause of death was violent in 54 cases (67.5%) and in 26 (32.5%) cases the death was unexpected, but it was due to medical reasons. There were no differences in age nor gender between these two groups of cases. Of 80 cases of renal tumors detected during autopsy, in 3 cases (3.75%) the tumor was metastatic from an extrarenal site. Of these, in one case the breast was the primary location, in one case the lung was the primary location, and in one case the primary location was uncertain. The most common histology among the primary tumors was clear cell (conventional) renal cell carcinoma, although its frequency was significantly lower than in usual surgical series. Significantly, the overall number of papillary tumors, namely adenomas and papillary carcinomas, almost reached the number of clear cell carcinomas. The specific diagnoses are shown in Table II, along with the average subjects' age. The differences in age of the patients with specific diagnoses were not statistically significant; of particular note is the quite similar age of the patients with the most prevalent histologic types (clear cell and papillary carcinoma, as well as renal adenoma). Somewhat surprisingly, the ages observed in the current series were not dissimilar from the ones observed in our surgical material (60.9 for clear cell carcinoma, 59.7 for papillary carcinoma, 60.0 for oncocytoma; unpublished data and [10-12]). There were some gender-related differences in the specific diagnoses: 30 out of 33 subjects with clear cell carcinoma, 13 out of 14 with papillary carcinoma and 14 out of 15 with adenoma, were males, however all 3 cases of angiomyolipoma were observed in females. There were some differences in diagnoses between persons dying of violent or medical reasons (Table III), but these did not reach statistical significance.

Table I. Primary antibodies used in the study

Specificity	Clone/type	Dilution
CK-HMW	34βE12	1 : 50
CK7	OV-TL 12130	1 : 50
CK	MNF116	1 : 50
CK19	RCK108	1 : 50
EMA	E29	1 : 100

Discussion

The methods to assess the real frequency of tumors may not be evident. Standard epidemiologic studies show only the incidence of symptomatic cases, and this may lead to biased results. Some tumors, such

Table II. Diagnoses made in the study

Diagnosis	N (%)	Age
clear cell carcinoma	33 (41.25%)	58.9
papillary carcinoma	14 (17.50%)	54.8
adenoma	15 (18.75%)	56.4
chromophobe carcinoma	1 (1.25%)	66
urothelial carcinoma	1 (1.25%)	75
oncocytoma	3 (3.75%)	76.7
unclassified carcinoma	6 (7.50%)	67.8
angiomyolipoma	3 (3.75%)	53.7
fibroma	1 (1.25%)	21
metastasis	3 (3.75%)	59.0

Table III. Diagnoses by cause of death

Diagnosis	Violent	Sudden Medical
clear cell carcinoma	25 (46.30%)	8 (30.77%)
papillary carcinoma	7 (12.96%)	7 (26.92%)
adenoma	12 (22.22%)	3 (11.54%)
chromophobe carcinoma	0	1 (3.85%)
urothelial carcinoma	1 (1.85%)	0
oncocytoma	2 (3.70%)	1 (3.85%)
unclassified carcinoma	3 (5.56%)	3 (11.54%)
angiomyolipoma	2 (3.70%)	1 (3.85%)
fibroma	1 (1.85%)	0
metastasis	1 (1.85%)	2 (7.69%)

as renal tumors, may tend to remain asymptomatic for long periods of time. In fact, currently most renal tumors are detected incidentally by imaging studies. The progress in accessibility and effectiveness of imaging may in part be responsible for the increased rate of detection of renal tumors. King *et al.* [13] analyzed United States cancer registers for RCC cancer incidence, and found a continuous increase. Interestingly the increase was most significant in a younger population; the increase was also more evident in females and concerned higher grade tumors. The authors explained this finding by increased obesity and tobacco smoking, which are both established risk factors. An unusual case is Sweden, where RCC frequency decreased since 1980. Lyrdal *et al.* showed that this is due to an actual decrease in incidence, followed by decrease in stage and grade of the tumors. There were however no histologic tumor type migrations [14]. The recognized phenomena are a decrease of stage and grade which are referred to as stage and grade migration, whereas the relative decrease of most aggressive histologic subtypes is referred to as type migration. Some interesting information about the epidemiology of cancer may be obtained from unselected autopsy material. Although anatomopathological autopsies are most frequently analyzed [4], it is difficult to regard them as entirely unselected; this is the why we decided to analyze forensic autopsies [7, 14-20].

Renal tumors are highly heterogeneous. The most frequent diagnostic categories include rather aggressive conventional renal cell carcinomas, papillary carcinomas, indolent chromophobe carcinomas, and most benign oncocytomas. Also within these categories, individual tumors may differ greatly in their biologic potential and growth rate. This will result in different odds of incidental detection versus symptomatic presentation. It is expected that the slowly growing and indolent tumors are likely to remain undetected along the patients' life; the real frequency of such lesions could be assessed by autopsy studies only. We [4] and the others [7, 14, 16, 18, 20, 21] have shown previously that the relative frequency of conventional (clear cell) carcinomas is much lower in such material and the frequency of papillary tumors (carcinomas and papillomas) is much higher than in surgical series. Our previous study was biased in a way, as we considered anatomopathological post-mortem material. The post-mortem examinations requested by the clinicians will obviously be performed on patients with primary conditions and causes of death that may influence the frequency of renal tumors (such as hypertension, diabetes or smoking-related conditions). Consequently, the current anatomopathological post-mortem examinations are becoming less representative of the entire hospitalized population. Even more importantly, we are experiencing a constant decrease in the rate of post-mortem examinations performed [22-24]. In our institution, the autopsy rate has dropped from 54.2% in 1979 to 15.3% in 2009 (unpublished data); an even more drastic decrease is seen in other studies [22, 25]. With a decreased autopsy rate, the indication for them will also change. This undoubtedly influences the structure of the available population examined in different periods of time. On the other hand, the forensic autopsy rate seems to remain rather constant over time [22]. Also, the population of patients undergoing forensic autopsies is different from the ones undergoing anatomopathogical autopsies, with an obvious overrepresentation of younger people dying prematurely by a sudden or violent death. In fact, the average age in the current series was 58 years, over 10 years less than in our previous study [4]. Thus, forensic autopsy material should give us a unique insight into the frequency and category of the structure of renal tumors, and this was the rationale behind the present study. In the present study, the frequency of renal tumors (0.54%) was much lower than in previous work (2.8%, $p << 0.01$). Also, the frequency of non-renal cancers was also significantly lower (30 vs. 3, $p << 0.01$). A potential limitation of the present approach might be limited interest for insignificant medical lesions during forensic post-mortem examination. However, it may be assumed that by rule, all grossly visible renal lesions were sampled. Analysis of the frequencies of specific histological subtypes showed characteristics intermediate between our previous post-mortem and surgical series. In particular, the frequency of papillary adenomas was much lower than in anatomopathological autopsy cases. Papillary adenomas are interesting as they are thought to be a precursor lesion for papillary carcinoma [26].This could be due to the intrinsic differences among forensic cases, as being younger may

be less prone to have chronic renal disease; chronic renal disease is known to be related to appearance renal adenomas [5]. Kihira *et al.* [18] detected 51 cases of renal carcinomas in 7970 autopsies performed (0.65%). The rate seen in our present study is significantly lower (0.54% renal tumors, but only 0.37% carcinomas). As the classification used by these authors is outdated, it is difficult to comment on the histologic types described. Surprisingly, very large proportion of incidental renal cell carcinomas were accompanied by cancers in another location; we haven't seen such a phenomenon neither in this, nor our precedent study [4]. Mindrup *et al.* [25] analyzed frequency of renal tumors in two periods, 1955–60 and 1991-2001. They found renal mass detection rate 3.4% and 2.3%, respectively, figures similar to our anatomopathologic material were reported in the precedent study [4]. While the overall number of renal tumors detected at autopsy decreased, the frequency of incidental renal carcinomas remained constant. Wunderlich *et al.* [20] analyzed frequency of necropsy-detected RCC in two Central-European regions, and found frequency of 1.76 and 1.55%, respectively. They found certain increase in frequency of incidental RCC and this increase paralleled the increase in the clinically evident RCC. This lead to the conclusion that the increase of clinically-evident cancer is due to an actual increase in frequency, and not just to better detection. In Iceland, Jonsson *et al.* [21] found much lower frequency of autopsy – detected renal carcinoma (0.71%). In their material the tumors were smaller and lower stage than surgical cases. Similarly in our studies, the frequency of papillary tumors was significantly higher in autopsy cases (21% vs. 8%). Mauermann *et al.* [27] analyzed the gender differences in frequency of benign renal tumors, and in females found significantly higher incidence of angiomyolipoma, while oncocytomas were more frequent in males. Similarly in our study all angiomyolipoma patients were females, while 2 out of 3 patients with oncocytoma were males. Of note, the diagnosis by imaging studies was benign in only 17% of cases in Mauermann's material. This is quite concerning, with a wider range of therapeutic options available, and may lead to increased interest in renal mass biopsy [19].

In conclusion, we have found that the frequency and histopathological types of renal tumors in forensic post mortem material are similar to that in anatomopathological post mortem material however some differences can be observed.

The authors thank Mr. Matthew Ficinski for help in editing the manuscript.

The authors declare no conflict of interest.

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Address for correspondence

Krzysztof Okoń MD PhD
Department of Pathomorphology
Jagiellonian University Collegium Medicum
Grzegórzecka 16
31-531 Krakow, Poland
e-mail: mpokon@cyf-kr.edu.pl