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REVIEW

Spontaneous regression of renal cell carcinoma: Reality or myth?

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Abstract

Spontaneous regression of a malignant tumor is a very rare phenomenon. Renal cell carcinoma (RCC) is an aggressive malignancy with an often unpredictable behaviour. The incidence of spontaneous regression in metastatic RCC has been estimated to lie between < 1% and 7%. The spontaneous regression of a primary RCC has been reported much less commonly. Our literature review assesses the published literature concerning spontaneous regression of either primary or metastatic RCC. In order to examine this phenomenon in more detail we performed a literature search in the PubMed Database using the Keywords "renal cell carcinoma", "metastatic disease", and "spontaneous regression" and included reports from the last 100 years. The incidence of spontaneous regressions in RCC has always been considered a special feature of RCC compared to other solid malignancies. The majority of case reports of spontaneously regressed RCC describe the regression of metastases after nephrectomy rather than the spontaneous regression of a primary tumor. In cases of reported regression of metastatic RCC, this mostly applied to pulmonary lesions. As possible reasons for spontaneous regressions host immune defense mechanisms against metastatic RCC tissue following nephrectomy are discussed as important factor. RCC is known to be highly immunogenic and the possible existence of cytotoxic serum factors and tumor-specific surface antigens may trigger a cell-mediated cytotoxicity as an immunological basis for regression. Histological verification of supposed regression of a primary tumor may cause diagnostic difficulties, since large central areas of necrosis and cystic lesions of the tumor can occur simultaneously. The well-known phenomenon of necrosis in a fast growing RCC at the time of nephrectomy must not be confused with true spontaneous regression. Therefore, in our opinion such reported cases of supposed partial spontaneous regressions of primary RCCs are highly questionable. Most cases of spontaneous regression of RCC metastases have been reported after nephrectomy as the only treatment. Debulking by tumor nephrectomy then gives the immune system the chance to cope effectively with the remaining much lower quantity of tumour antigens. However, the mechanisms leading to spontaneous regression of metastatic lesions after cytoreductive nephrectomy are still poorly understood.

Key words: Renal cell carcinoma; Spontaneous regression; Primary renal cell carcinoma; Metastatic renal cell carcinoma lesions; Cytoreductive nephrectomy

Core tip: Renal cell carcinoma (RCC) is an aggressive malignancy, which, from an immunological point of view, is highly variable. In the era of immunotherapy for metastatic RCC with interferon or interleukin it was always emphasized that spontaneous remissions of RCC, although comparatively rare, do occur and support the use of immunological therapies in metastatic disease. However, we suspected that this frequently cited occurrence of spontaneous remissions is more

legend than reality. We therefore undertook an extensive literature search and included reports from the last 100 years in order to evaluate the scientific evidence describing spontaneous regressions of primary or metastatic RCC.

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INTRODUCTION

Spontaneous regression of a malignant tumor must by necessity be considered a very rare phenomenon. One of the first reported cases was that of a soft tissue sarcoma described by Coley[1] in 1893. In a historic study from 1918, 302 cases of spontaneous tumor regressions were described with only one case of a renal tumour among them[2].

Renal cell carcinoma (RCC) is an aggressive malignancy with an often unpredictable behaviour. At the time of diagnosis, about one third of all patients will already have metastases and another third will develop metachronous metastatic disease after surgery[3].

As early as 1928, Bumpus[4] reported the first case of a spontaneous regression of metastatic RCC. Further reports of spontaneous regressions of metastatic RCC have mostly been those of pulmonary RCC metastases, which supposedly regressed after radical nephrectomy. The incidence of spontaneous regression in metastatic RCC has been estimated to lie between < 1% and 7%[5,6]. However, the spontaneous regression of metastatic RCC lesions has also been reported for brain, bone, adrenal and liver metastases[7].

The spontaneous regression of a primary RCC has been reported much less commonly. However, underlying hypothetical mechanisms for spontaneous regression, which have been mentioned in the literature include humoral, immunological and vascular factors, *e.g.*, autoinfarction[8,9].

In the reported cases of spontaneous regression, the duration of disease remission is either relatively short or has not been reported at all. The longest reliably observed durations of regression of metastatic RCC lasted for 10 years[10] and for over 20 years[5]. Our literature review assesses the published literature concerning spontaneous regression of either primary or metastatic RCC.

LITERATURE SEARCH

A literature search was performed in the PubMed Database using the Keywords "renal cell carcinoma", "metastatic disease", and "spontaneous regression" and included reports from the last 100 years.

RESEARCH

Spontaneous regression of a malignant tumor or its metastases has been defined as a partial or total disappearance of disease without any treatment or induced by local treatments or interventions like embolisation of the primary tumor. The incidence of spontaneous regressions in RCC has usually been reported to be about 1% and this has always been considered a special feature of RCC compared to other solid malignancies. However, the natural course of RCC is not always predictable and includes spontaneous regression of pulmonary metastases following nephrectomy, prolonged survival and stable disease, late relapse after nephrectomy and poor long term outcome despite spontaneous regression[11]. Spontaneous regression is not synonymous with cure, as later recurrences have been reported[12,13]. Thus, a patient cannot be considered cured even if spontaneous regression is suspected if an RCC has been diagnosed[14].

Possible causes of spontaneous regression

Following nephrectomy, it is conceivable that host immune defense mechanisms against metastatic RCC tissue may be activated. Everson *et al*[12] in 1966 postulated such an immune mechanism as the most important factor for spontaneous regression of cancer.

Clinical observations seem to support this hypothesis and several examples for the relationship between neoplastic disease and the function of the immune system exist such as the incidence of lymphomas in patients with AIDS or after organ transplantation, the regression of Kaposi's sarcoma after withdrawal of immunosuppressive therapy[15-18] and the generally increased risk of cancer development with immunosuppression after organ transplantation[19]. As a possible reason some authors postulated a lack of immuno-surveillance of virus-transformed cells by strong immunosuppression. That may lead to an increased frequency of viral infections and/or virus-induced malignancies. Nevertheless, other types of malignant tumors, which are not associated with viral infections, are frequently increased in transplant recipients, too, in dependence of the duration of exposure to immunosuppression[19].

RCC is known to be highly immunogenic and the possible existence of cytotoxic serum factors and tumor-specific surface antigens may trigger a cell mediated cytotoxicity as an immunological basis for regression[20,21]. The majority of case reports of spontaneously regressed RCC describe the regression of metastases after nephrectomy rather than the spontaneous regression of a primary tumor. In malignant melanoma, studies analyzing the T-cell response in regressive primary melanoma in comparison to the metastatic lesions have found a major difference in the number of T-cells in the regressed primary and in metastatic lesions[22].

In cases of reported regression of metastatic RCC, this mostly applied to pulmonary lesions. The constant antigenic stimulation to which the lungs are exposed and

the high quantities of macrophages, lymphocytes and immunoglobulin IgA present in pulmonary tissue have been discussed as possible factors explaining such a phenomenon[23-25]. In contrast, the spontaneous regression of brain metastases has rarely been reported and this has been explained with the blood-brain-barrier limiting an immune response because of a lack of lymphocytes infiltrating the brain tissues compared to other organs and tissues[26]. Thus, hypotheses explaining observed immunological responses against malignant lesions in different sites are available.

This theory of an underlying immune mechanism has been proposed by several authors[27,28]. A remarkable report is that by Horn *et al*[26] (1971) about the induction of an RCC regression in a patient with metastatic disease after the transfusion plasma from another patient of the same family who had experienced spontaneous regression. The authors suggested "some sort of host resistance" in this case, mainly a plasma-related transfer factor, an interferon-like agent or a kind of cytotoxic antibody or a substance mediating cellular immunity[27].

In contrast, the generally poor response of metastatic RCC to immunotherapy is perhaps an argument not supporting the general importance of immunological mechanisms.

From reported experience with other malignancies which have undergone spontaneous regression (neuroblastoma, malignant melanoma, malignant lymphoma and leukemias), several other factors have been proposed as underlying mechanisms such as growth factors and/or cytokines, the induction of differentiation, endocrine mechanisms, the elimination of a carcinogen, tumor necrosis, apoptosis and/or the inhibition of angiogenesis and epigenetic mechanisms[29]. This number of proposed mechanisms just underscores the fact very little is actually known about spontaneous regression and/or that different mechanisms may be of importance in different cases[10,29,30]. For example, cytokine production by the tumor itself or by host tissue has been postulated to be involved in regressions of RCC because in one reported case of regressed intrathoracic metastases elevated serum levels of interleukin 2 receptor were reported[31].

Necrosis and apoptosis both occur in RCC and result in cell death. Gross central tumour necrosis is often clinically and pathologically seen in large and rapidly growing RCCs. This is usually considered as indicating that the rapid growth outgrowths the tumour's blood supply. Interestingly, synchronous necrosis within the primary tumor and in the metastatic lesions of RCC seems to be very rare. Boasberg *et al*[25] (1996) reported such a case of RCC with a caval thrombus and the spontaneous regression of pulmonary metastases. After resection of the primary tumor and the thrombus, histological examination verified necrosis at both sites.

Apoptosis, programmed cell death, has also been suggested to be an underlying mechanism of spontaneous regression in RCC. Pansera[31] (1992) postulated spontaneous RCC regression to be a re-expression of cell death programs typical for renal tissues since pronephros and mesonephros undergo complete regression during embryogenic renal development. Such an embryological cell death program could hypothetically be reactivated in immature RCC tissue. Indeed, the manifestation of embryological cell characteristics does occur in many neoplasms[32]. This phenomenon of morphological similarities between growing tissues, like embryological and cancer cells has its reasoning in a common origin from a precursor stem cell. Thus, spontaneous regression of RCC may be explained as a kind of re-expression of embryonic features by adult carcinoma[32].

Histological verification of regression

In a primary RCC: Histological verification of supposed regression of a primary tumor may cause diagnostic difficulties, since large central areas of necrosis and cystic lesions of the tumor can occur simultaneously. Therefore, the differential diagnosis of a spontaneously regressed RCC should include inflammatory lesions of the kidney, *e.g.*, xanthogranulomatous pyelonephritis, sinus histiocytosis and tuberculosis or malakoplakia. This requires an extensive tissue sampling by the pathologist to confirm or refute the diagnosis of spontaneous regression of an RCC[33].

In our review of the literature we found only 7 reported cases of partial or total spontaneous regression of primary RCCs (Table 1). However, in most of these seven cases the regressions were not unequivocally confirmed.

The first documented case of a total spontaneous regression of a primary RCC was reported by Choi *et al*[33] in 1986. The authors diagnosed a left sided renal tumor and performed a nephrectomy. Histologic examination revealed a cyst-like capsule with coagulated blood, necrotic tissue, calcifications and a cluster of tumor cells, which were classified as a spontaneously regressed primary RCC.

Hamid *et al*[32] in 1998 described two similar cases, one with a cystic cavity of the kidney "containing necrotic debris and brown fluid occupying virtually the whole of the specimen" and "occasional foci of viable renal cell carcinoma …seen in the capsular area". These findings were deemed to represent spontaneous regression by the authors. However, the differential diagnosis must include a developing RCC within a cystic renal lesion with previous hemorrhage. The second case reported by Hamid *et al*[32] should also be viewed critically. There they found "an extensively involuted/hyalinised lesion with extensive metaplastic ossification and also foci of dystrophic calcification" and, again, "occasional foci of cells with clear cytoplasm". Neither of these two case reports included any follow-up information at all[33].

More stringently, spontaneous regression of an RCC or its metastases should be defined as a partial or complete regression of a renal neoplasm which has been histologically confirmed first and then regressed either without treatment or sometimes following an intervention, *e.g.*, cytoreductive nephrectomy. It is important to note that it

Table 1 Regression of primary renal cell carcinoma

Case	Year	Type of regression	Histology documented	Follow up (interval)
Hall[53]	1908	Total regression (?)	Entirely necrotic tumor	Not given
Choi *et al*[33]	1986	Total regression (?)	Cyst-like capsule with necrotic tissue Calcifications and a cluster of tumor cells…	Not given
Edwards *et al*[34]	1996	Partial regression	Residual RCC with marked fibrosis And calcification	36 mo
Hamid *et al*[32]	1998	"Extensive regression"	Extensively hyalinised lesion, also foci Of cells with clear cytoplasm	Not given
			Cystic cavity containing necrotic Debris, occasional foci of viable RCC	Not given
Lacquaniti *et al*[35]	1999	Partial regression	Fibrotic involution….. With few central areas of RCC	7 mo
Kobayashi *et al*[8]	2002	Partial regression of primary RCC with inferior V. cava Tumor thrombus	No	2 yr

RCC: Renal cell carcinoma.

is possible to find necrosis in a fast growing RCC at the time of nephrectomy and this well-known phenomenon must not be confused with true spontaneous regression. However, some authors do consider such a necrosis as a partial regression[34-36]. Thus, in our opinion such reported cases of supposed spontaneous regressions of primary RCCs are highly questionable (Table 1).

In metastatic RCC lesions: In all, we found 94 reported cases of spontaneous regression of metastatic lesions in patients with an RCC (Table 2). Most of these reports concern pulmonary metastases (75 cases) and only a few other sites: pleura and mediastinum (3), liver (4), pancreas (1), brain (3), bone (5), eyes (2) and skin (1) (Table 2). Most of these case reports give no histological verification of the supposedly metastatic lesions. Thus, the diagnosis of spontaneous regression was based on changes in size on imaging which therefore cannot be considered as a proof beyond doubt.

Kavoussi *et al*[36] reported a rate of regression of 20% based on diagnosis by cytology. However, Davis *et al*[37] found a regression of pulmonary RCC metastases in only 3/14 documented cases, *i.e.*, unrelated to any kind of treatment including nephrectomy[38].

In evaluating spontaneous regression of a primary tumor as well as metastatic lesions, histological verification can be a diagnostic challenge. Patients with advanced metastatic disease are often not in good general condition for any surgical or interventional procedures. Edwards *et al*[34] (1996) pointed out that fine needle biopsy carries a risk of gross bleeding due to blood coagulation potentially affected by paraneoplastic mechanisms. Furthermore, computed tomography (CT)-guided biopsies may be unsuccessful in rendering good histologic reports because of insufficient sample size.

In case of eye or brain lesions, cytological or histological verification is even more difficult and dangerous. Thus, in clinical practice such procedures are usually avoided when the primary tumor has been histologically confirmed as an RCC[39-41].

Thus, in cases without convincing histological evidence of pulmonary RCC metastases, several other benign conditions must be considered in the differential diagnosis, such as fungal or mycobacterial infections, sarcoidosis, Wegener granulomatosis and vasculitic lesions which can all appear as pulmonary lesions and regress later[38]. In the pre-CT era, the misinterpretation of radiological findings in conventional chest X-ray studies may have been more common than appreciated at the time. Thus, cases diagnosed as spontaneous regression of RCC metastases in the lungs by chest x-ray only should also be regarded with caution. Furthermore, even cases of pulmonary RCC lesions by cytology or even histology which then had spontaneous regression diagnosed by chest X-ray only must be questioned in retrospect[42]. Embolisation of the lung or a pulmonary segment by tumor thrombi from the renal vein may cause regional pulmonary infarction, which may have the radiological appearance of metastatic lesions. The disappearance of these findings after improvement of inflammatory lesions close to such an embolus could also be misinterpreted as a spontaneous regression[43,44].

Cytoreductive nephrectomy

More than 40 years ago, Markewitz *et al*[44] advocated a palliative nephrectomy only to be considered in individually selected cases with careful evaluation of the potential benefit. However, since then a markedly longer survival has been shown in patients with RCC after nephrectomy and metastasectomy[45,46]. Therefore, the concept of cytoreductive nephrectomy should today be taken into consideration in all patients with metastatic RCC when the short-term outcome of the surgical procedure can be predicted to be acceptable[47].

Indeed, most cases of spontaneous regression of RCC metastases have been reported after nephrectomy as the only treatment. Two possible hypotheses have been put forward as explanations for this phenomenon:

First, a dissemination of tumor cells into the systemic circulation and the lymphatic system induced by the surgical procedure results in a large and ubiquitous presentation of tumor antigen and this may initiate a strong anti-

Table 2 Regression of metastases from renal cell carcinoma

Site of metastases	Source	Number of cases	Histological documentation	Follow up (interval)
Lung	Meinders[54]	1	No	3 yr
	Boasberg *et al*[25]	1	No	2.5 yr
	Cited by Freed *et al*[23]	45 (from 1928-1976)	13/45	
	Vizel *et al*[55]	1	No	11 mo
	Mohr *et al*[56]	1	No	22 mo
	Snow *et al*[5]	1	Yes	6.5 yr
	Nakano *et al*[57]	1	No	8 yr
	Barré *et al*[58]	2	Yes	5 yr
	Kavoussi *et al*[36]	1	Yes (cytologically)	6 yr
	Eissler[59]	1	Yes	7 yr
	Omland *et al*[60]	1	No	14 mo
	Davis *et al*[37]	1	Cytologically	18 mo
	de Riese *et al*[14]	2	No	5.5-11 yr
	Vogelzang *et al*[61]	1	Yes (cytologically)	5 yr
	Palmer *et al*[62]	1	No	15 mo
	Garcia-Del-Muro *et al*[63]	1	No	1 yr
	Czaplicki *et al*[64]	1	Not given	16 yr
	Marcus *et al*[65]	4	No	1-4.5 yr
	MacManus *et al*[30]	1	Yes	9 mo
	Bos *et al*[24]	1	No	1 yr
	Edwards *et al*[34]	1	No	36 mo
	Lokich[7]	1	No	2 yr
	Rauh *et al*[66]	1	Yes	8 mo
	Chang *et al*[11]	1	Yes	16 mo
	Sánchez-Ortiz *et al*[67]	1	Yes	10 mo
	Lekanidi *et al*[29]	1	No	5 mo
Bone	Mims *et al*[68]	1	Yes	1 yr
	Doolittle[69]	1	Yes	4 yr
	Freed *et al*[23]	1	Yes	10 yr
	Kerbl *et al*[70]	1	Yes	13 mo
	Nakajima *et al*[71]	1	Yes	8 mo
Pleural/mediastinal	Kallmeyer *et al*[72]	1	Yes	3 mo
	Abubakr *et al*[27]	1	Yes	1.5 yr
	Thoroddsen *et al*[49]	1	Yes	9 yr
Liver	Deweerd *et al*[73]	1	Yes	6 mo
	Ritchie *et al*[74]	1	Yes	9 mo
	Wyczólkowski *et al*[75]	1	Yes	12 mo
	Christophersen *et al*[10]	1	Yes	5 yr
Pancreatic choroidal	Altschuler *et al*[76]	1	Yes	2.5 yr
	Langmann *et al*[38]	1	No	6 mo
	Hammad *et al*[40]	1	No	
Brain	Omland *et al*[60]	1	No	14 mo
	Guthbjartsson *et al*[39]	1	No	9 yr
	Hensiek *et al*[77]	1	No	4 yr
Skin	Chang *et al*[11]	1	No	16 mo

tumoral immune response by the host. Secondly, because of the mass of tumour antigen is located in the primary tumor, debulking by tumor nephrectomy then gives the immune system the chance to cope effectively with the remaining much lower quantity of tumour antigens and thus to mount an effective antineoplastic response[13,14].

Although the morbidity and mortality of nephrectomy should always be taken into consideration, a palliative cytoreductive nephrectomy in metastatic RCC may also be beneficial for other reasons: in terms of the prevention of tumor toxicity, for the correction of hypercalcaemia and for the improvement of local symptoms, such as pain or hematuria[40,48-53].

Regression has also been described to occur after other local treatments such as radiotherapy or embolisation of the primary tumor[7,37,38,48-50].

CONCLUSION

Spontaneous regression in renal cell carcinoma is very rare and there probably has been an overreporting in the literature. However, it has been described plausibly in metastatic RCC sites-mostly pulmonary-and then mostly after nephrectomy, thus supporting the concept of cytoreductive nephrectomy. Despite several plausible hypotheses, the mechanisms leading to spontaneous regression of metastatic lesions after cytoreductive nephrectomy are still poorly understood.

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