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Responses of Renal Cell Carcinomas to 29 Different Systemic Anti-Cancer Therapies

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ABSTRACT

Introduction: The prevailing view is that renal cell carcinomas (RCCs) are resistant to chemotherapy. However, it is essential to periodically reassess paradigms. When RCC is diagnosed concurrently with another malignancy, the latter typically assumes priority in treatment. This scenario provides a unique opportunity to observe the effects of systemic therapy on the RCC, without incurring additional costs or risks to the patient. Our study aimed to explore the response of several "old school" and modern anti-cancer systemic therapies on growth rate of otherwise untreated RCC.

Methods: Twenty patients (average age 61.4 years, SD 10.0 years) were diagnosed with histologically confirmed RCC and another type of cancer. These included lymphomas (7 patients), lung adenocarcinoma, and breast cancer (4 patients each), leukemia (3 patients), and 4 patients with other types of malignancy. The cohort received 29 different systemic chemotherapeutic agents, including cyclophosphamide and doxorubicin (5 patients each), and prednisone, vincristine, and rituximab (4 patients each). The patients were monitored radiographically, focusing on RCC, without any RCC-specific treatments. Changes in RCC diameter on axial CT scans were recorded during the follow-up period.

Results: The average RCC diameter on initial CT scans was 41.9 ± 25.1 mm. After an average follow-up of 28.9 ± 29.6 months, the RCC diameter increased in 14 patients (by an average rate of 7.3 ± 2.9 mm/year), while it remained stable or decreased in six patients. Notably, tumor size reductions were observed in patients treated with Tamoxifen and a combination of bevacizumab, docetaxel, and cisplatin.

Conclusions: These results underscore the significant resistance of RCC to both traditional chemotherapies and newer treatments, many of which have not been specifically evaluated in the context of RCC. However, several agents demonstrated potential efficacy and merit further investigation. Nevertheless, no solid conclusion can be drawn regarding any specific agent using this methodology.

Keywords: Renal carcinoma, chemotherapy, immunotherapy, response rate

Introduction

Over a third of patients with renal cell carcinoma (RCC) present with metastatic disease or develop metastases after surgery for an apparently localized disease.[1] The prognosis for these patients is grim.

RCC is considered chemoresistant. In the metastatic setting, its response to single or combined chemotherapy agents has been examined in several phase I/II studies.[2] Single agents, including vinca alkaloids, gemcitabine, and fluoropyrimidine derivatives, have shown an objective response rate (ORR) of 0-20%. One study reported an ORR of 26% with capecitabine.[3] Combination chemotherapies, typically involving gemcitabine and fluorouracil, have not been more successful, with one study reporting a partial response in only 3 out of 30 RCC patients.[4] Immunotherapy with interleukin 2 or interferon alpha has shown an ORR of 10-15%, with occasional patients experiencing complete and durable responses. However, combining immunotherapy with chemotherapy (fluorouracil, gemcitabine, or vinblastine) has not significantly improved outcomes, though it has facilitated the reduction of immunotherapy doses.[5]

In the early 21st century, targeted therapies became the standard of care for metastatic RCC. These therapies include multi-kinase inhibitors (MKIs), mammalian target of rapamycin inhibitors (mTOR inhibitors), and vascular endothelial growth factor (VEGF) inhibitors.[6] However, the outcomes with these medications are disappointing, with progression-free survival rates of less than one-year, overall survival rates of less than two years, and significant side effects. One of the reasons for these poor outcomes is the heterogeneity of RCC, which includes inter-patient, intra-patient, intra-tumoral, and temporal components. Addressing this heterogeneity requires a flexible approach that chemotherapy and kinase inhibitors lack, but which the immune system possesses. Programmed Death Ligand 1 (PD-L1) is overexpressed in RCC, and currently, immune checkpoint inhibitors (ICIs) became the mainstay in treating metastatic RCC, showing superiority over MKIs.[6,7] For example, the CheckMate 214 showed that overall survival and objective response rates are significantly better with nivolumab plus ipilimumab compared to sunitinib in patients with intermediate- and poor-risk advanced clear cell RCC.[8] Similarly KEYNOTE-426 showed that pembrolizumab plus axitinib provide better response rate, progression-free survival and overall survival with similar toxicity compared to sunitinib in patients with advanced RCC.[9] Yet the overall survival with ICIs is far from satisfactory. The 5-year overall survival probabilities of patients with advanced RCC in CheckMate 025 was 26% with nivolumab, fueling a search for more efficient treatments.[10]

When any malignant tumor is diagnosed, a whole-body metastatic workup, usually in the form of CT, MRI, or PET-CT, follows. If this workup reveals a kidney mass, the question arises whether this mass is a primary tumor or a metastasis. A biopsy of the renal mass usually provides an accurate diagnosis.[11] Considering the indolent nature of RCC, in most cases, the other malignancy takes priority in treatment over the RCC.[12-16] This situation provides an opportunity to evaluate the response of RCC to various therapeutic agents without any additional cost or risk to the patient.

Materials and Methods:

The effects of systemic anti-cancer therapies, not targeted at RCC, were retrospectively evaluated through an archival search for patients with diagnosis of RCC (ICD-9-CM 189.0) and another type of cancer (ICD-9-CM codes 140-239). The initial search yielded 746 results. Patients included in the study met all the following criteria:

1. Histologically confirmed non-renal cancer.
2. Histologically confirmed RCC.
3. A CT scan performed before the initiation of systemic therapy, showing measurable RCC.
4. Undergoing chemotherapy or immunotherapy directed at the non-renal cancer, while the RCC received no specific treatment.
5. Subsequent CT scans conducted at least four months after therapy commencement.

The largest diameter of the RCC from the initial CT scan was recorded and compared with the measurements taken at the same location at the end of the follow-up period. Renal pathological specimens were evaluated using the 2002 TNM classification, histologic subtyping according to the 1997 UICC classification, and grading based on Fuhrman's nuclear grading system.[17-19] The tumor's linear growth rate was calculated by subtracting the tumor's largest diameter in the initial CT (mm) from the largest diameter on the last CT (mm), then dividing by the time elapsed between the studies (in years). Diameter changes within a 3 mm range were classified as "no change". The research was approved by the local ethical committee (#302-19-HMO) that waved the requirement for informed consent.

Results

PATIENTS

Demographics, types of malignancy, and systemic therapy protocols of the 20 patients that met all criteria are detailed in Table 1. The cohort consisted of 14 men and 6 women, with an average age at diagnosis of 61.4 years (SD 10.0 years). Cancer types included lymphoma in 7 patients, lung adenocarcinoma and breast cancer in 4 patients each, and leukemia in 3 patients. Each of the following was present in one patient: colon cancer, melanoma, gastrointestinal stromal tumor, and carcinoma of the gastrointestinal junction. One patient had three types of malignancies (patient #8). After a median follow-up of 56.5 months (Q1 38.75, Q3 97.75), eleven patients died, all from their non-renal cancers.

SYSTEMATIC TREATMENTS

Patients received a total of 29 preparations, administered either as single agents or in combinations. CHOP or R-CHOP combinations were administered to 4 patients. Other commonly prescribed agents included cyclophosphamide and doxorubicin, each given to 5 patients, and vincristine to 4 patients. The complete list of medications is available in Supplementary Document 1.

RENAL CELL CARCINOMA DIRECTED TREATMENTS

Treatments directed at RCC and the patients' statuses at the end of the follow-up period are shown in Table 2. By the end of the follow-up, 6 patients had undergone radical nephrectomy, 5 had partial nephrectomy, 3 had percutaneous ablation, and one patient had main renal artery embolization (to control bleeding). Five patients received no specific RCC-directed therapy.

RESPONSE OF RENAL CELL CARCINOMA TO SYSTEMIC THERAPY

RCC diameters, time intervals, and growth rates are detailed in Table 3 and Fig. 1. Representative CT images are presented in Fig. 2. The complete set of photos and case histories is available in Supplementary Material 2. The average RCC diameter on the initial CT was 41.9 mm (SD 25.1 mm). After an average follow-up of 28.9 months (SD 29.6 months), the RCC diameter increased in 15 patients (by an average growth rate of 7.3 mm/year, SD 2.9 mm/year). In patients treated with CHOP or R-CHOP, the average growth rate was 8 mm/year (SD 3.0 mm/year). In those treated with cyclophosphamide or doxorubicin, the average growth rate was 5.9 mm/year (SD 4.5 mm/year), and in patients treated with vincristine, the average growth rate was 6.3 mm/year (SD 5.1 mm/year). The RCC diameter remained stable in four patients and decreased in two patients (by 12 mm/year in a tamoxifen-treated patient and by 3.1 mm/year in a patient treated with a combination of bevacizumab, paclitaxel, and cisplatin).

Table 1: Patient demographics, other malignancy types, and treatment regimens

Num	Age*	Sex	Charlson Comorbidity index*	Metastasis*	Other Malignancy	treatment regimen**
1	57	F	6	Y	Breast Cancer	trastuzumab, pertuzmab
2	60	M	2	N	Diffuse large B-cell lymphoma	CHOP, rituximab etoposide
3	68	F	7	Y	Prim effusion Lymphoma	CHOP, rituximab
4	58	M	6	Y	Diffuse large B-cell lymphoma	R-CHOP
5	68	M	7	N	Gastrointestinal stromal tumor	imatinib
6	84	M	6	Y	Colon cancer	capecitabine
7	59	M	3	N	Lung adenocarcinoma	cisplatin, Vinorelbine
8	61	M	4	N	Acute myelocytic leukemia, Lung adenocarcinoma, Diffuse large B-cell lymphoma	ruxilitinib azacitidine, venetoclax
9	40	M	2	N	Mantle cell Lymphoma	R-CHOP
10	61	M	2	N	Marginal zone Lymphoma	bendamustine, rituximab
11	64	F	2	N	Breast cancer	doxorubicin, methotrexate, cyclophosphamide, docetaxel
12	81	M	6	Y	Lung adenocarcinoma	vinorelbine
13	50	M	6	Y	Gastro-esophageal junction tumor	docetaxel oxaliplatin fluorouracil
14	50	F	6	N	Breast cancer	anastrozole
15	61	M	2	N	Hodgkin's disease	BV-AVD
16	63	F	2	N	Chronic Lymphatic Leukemia	vincristine fludarabine, cyclophosphamide
17	62	M	6	N	Lung adenocarcinoma	bevacizumab, docetaxel, cisplatin
18	67	M	8	Y	Melanoma	dacarbazine, ipilimumab
19	64	M	2	N	Acute myelocytic leukemia	HiDAC
20	50	F	6	Y	Breast cancer	tamoxifen

*During diagnosis of RCC

**BV-AVD: brentuximab-vedotin, doxorubicin, vinblastine, dacarbazine

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

HiDAC: High dose cytarabine

Table 2: Renal cell histology, follow-up periods and final status

Num	Histology	What was done with RCC	Last follow-up of RCC	Kidney Status*	Last follow-up of other Malignancy	Other Malignancy status*
1	Clear F1	Partial nephrectomy	35	Alive NED	38	Alive SD
2	Clear F2	Partial nephrectomy	131	Died NED	131	Died Lymphoma
3	Clear F2	Not treated	65	Died PD	65	Died Lymphoma
4	Clear 3	Radical nephrectomy	40	Died NED	40	Died Lymphoma
5	Clear 2	Percutaneous ablation	123	Alive NED	123	Alive NED
6	Clear 2	Percutaneous ablation	46	Died NED	46	Died chondrosarcoma
7	Clear 1	Radical nephrectomy	15	Died NED	15	Died lung
8	Papillary	Not treated	97	Died NED	97	Died Leukemia
9	Clear 2	Not treated	10	Died PD	10	Died Lymphoma
10	Papillary	Radical nephrectomy	156	Alive NED	156	Alive NED
11	Clear 1	Partial nephrectomy	60	Alive NED	84	Alive NED
12	Papillary	Embolization only	76	Died PD	76	Died lung
13	Clear 2	Radical nephrectomy	60	Alive NED	60	Alive SD
14	Clear 4	Radical nephrectomy	53	Died NED	53	Died breast
15	Papillary	Partial nephrectomy	22	Alive NED	25	Alive SD
16	Clear (no specific grade)	Percutaneous Ablation	71	Died NED	168	Died Leukemia
17	Clear 1	Not treated	27	Died PR	27	Died lung
18	Papillary	Radical nephrectomy	100	Alive NED	100	Alive NED
19	Clear 2	Partial nephrectomy	51	Alive NED	51	Alive NED
20	Clear 2	Not treated	40	Died PD	40	Died breast

*NED- no evidence of disease

SD- stable disease

PD- progressive disease

Supplementary material 1

List of ICD-9-CM codes used for search:

RCC- 189.0

Lung cancer – 162.9

Breast cancer- 174.9

Lymphoma 202.8

Leukemia 153.9

Malignant melanoma 172

Stomach cancer 151.0, 151.9

Table 3: Renal cell carcinoma diameters, follow-up times, and growth rates

Num	Diameter 1 (mm)	Diameter 2 (mm)	Time difference (months)	Growth rate (mm/year)
1	31.8	42.3	12	10.5
2	10.3	50.3	71	6.7
3	35.6	56.6	43	5.8
4	43.0	49.1	11	6.6
5	21.7	32.4	25	5.1
6	36.4	42.3	7	10.1
7	22.9	25.1	6	4.4
8	20.1	63.8	97	5.4
9	71.1	81.2	10	12.1
10	29.6	40.2	28	4.5
11	27.1	31.5	12	4.4
12	93.6	123.8	49	7.4
13	73.1	75.4	4	6.9
14	94.0	97.9	4	11.7
15	31.2	31.2	11	0.0
16	11.2	34.2	75	3.68
17	51.6	47.8	27	-3.1
18	23.3	32.5	78	1.4
19	47.6	47.6	4	0.0
20	63.1	60.1	4	-12.0

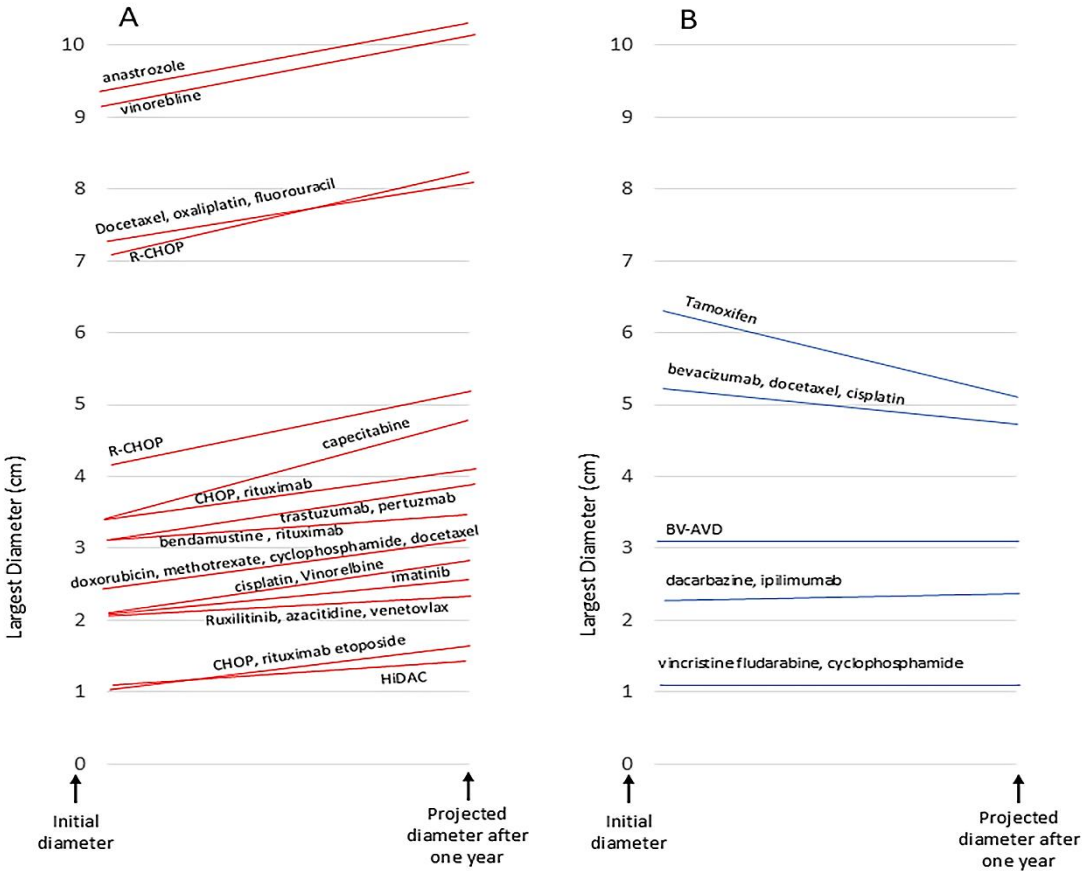

Fig. 1. Annual diameter change rates under various treatments. A: Tumors that increased in size; B: Tumors that remained stable or decreased in size.

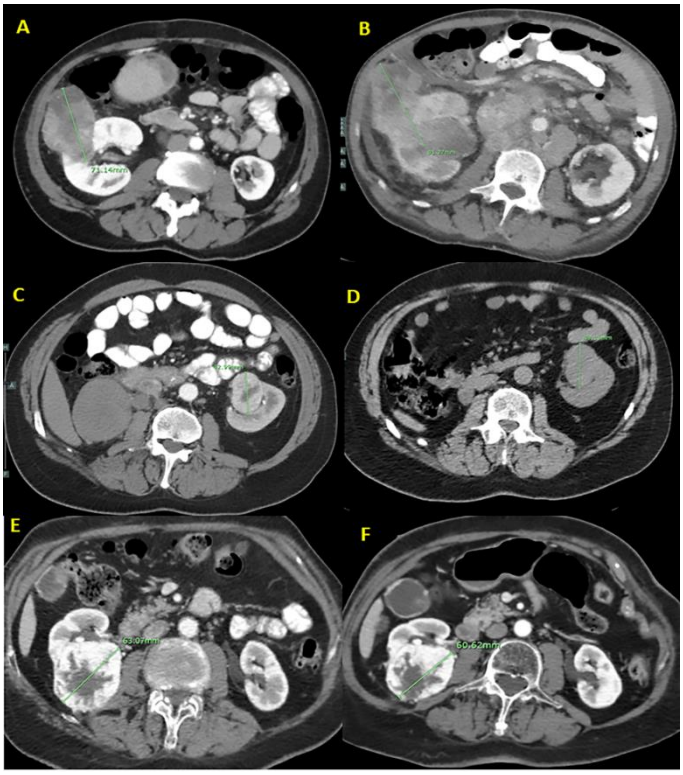

Fig. 2. A: A 40-year-old man diagnosed with mantle cell lymphoma and Fuhrman grade 2 clear cell carcinoma. B: After 10 months and 4 cycles of R-CHOP, the tumor's diameter increased by 10 mm.
C: A 58-year-old man diagnosed with diffuse large B-cell lymphoma and Fuhrman grade 3 clear cell carcinoma. D: After 11 months and 6 cycles of R-CHOP, the tumor's diameter increased by 6 mm.
E: A 50-year-old woman with breast cancer and Fuhrman grade 2 clear cell carcinoma. F: After 4 months of tamoxifen, the tumor's diameter decreased by 2.5 mm.

Supplementary material 2

Medications list (number of patients treated)

aenetoclax
anastrozole
azacitidine
bendamustine
bevacizumab
brentuximab vedotin
capecitabine
Cisplatin (2)
cyclophosphamide (5)
dacarbazine (2)
docetaxel (2)
doxorubicin (5)
etoposide
Fludarabine
fluorouracil
high-dose cytarabine
imatinib
ipilimumab
methotrexate
oxaliplatin
pertuzmab
prednisone (4)
rituximab (3)
rituximab (4)
tamoxifen
trastuzumab
vinblastine
vincristine (4)
vinorelbine

Discussion

In this study, we evaluated the effects of 29 systemic anticancer medications on RCC growth rates in the absence of specific anti-RCC therapy. These medications included some of the most aggressive combinations in hemato-oncology (CHOP and R-CHOP) and some of the latest anticancer agents, such as modern chemotherapeutics, monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates. The general response of RCC to systemic treatment was disappointing. In 14 out of 20 patients, the RCC diameter increased during follow-up (by an average of 6.9 mm/year). Specifically, in the 4 patients treated with CHOP or R-CHOP, the average diameter increase was even higher (8 mm/year), and in the 5 patients treated with cyclophosphamide or doxorubicin, it was 5.9 mm/year.

Are these growth rates typical for untreated RCC, or does chemotherapy had some effect on tumor's growth rate? Much of the literature on the growth rate of untreated RCC stems from surveillance studies in patients with solid-enhancing renal masses. A meta-analysis of 10 studies involving 234 patients with untreated enhancing renal masses reported an average growth rate of 3 mm/year.[12] This figure might underestimate the actual growth rates as it is based on evaluations of small tumors (average diameter of 2.6 cm at presentation) in elderly patients (average age 71 years) without histological confirmation in many cases. However, the growth rate in patients with histologically confirmed RCC was not significantly higher (4 mm/year). When larger tumors were monitored, the growth rate was remarkably similar to the rates observed in the current series (5.7-8.0 mm/year).[20,21] Thus, it is reasonable to conclude that most anticancer medications administered in the current study did not modify the natural growth of RCC.

Several mechanisms have been associated with RCC's resistance to chemotherapy among them are: Overexpression of p-glycoprotein MDR1/ABCB1 transporters that actively pump chemotherapeutic agents out of the cells.[22] Rapid drug inactivation through enhanced cytochrome p450 CYP1B1 activity that leads to drug inactivation before cellular damage is done.[23] Hypoxic induced deactivation of p53. This is facilitated by the loss of the von Hippel-Lindau (VHL) tumor suppressor protein, leading to Hdm2-mediated suppression of p53.[24] Additionally, dysregulation of the PI3K/AKT/mTOR

pathway, frequently observed in RCC, leads to the downregulation of anti-angiogenic factors like thrombospondin-1, contributing to this phenomenon.[25] Changes in the detoxification pathway for reactive oxygen within the glutathione redox cycle and activation of the ATP-dependent drug efflux pump via the membrane-bound P-170 glycoprotein also contribute to the primary resistance of chemotherapy in RCC models.[26]

In four patients, RCC diameter remained stable during follow-up, and in two patients, it decreased. The most significant case of shrinkage involved a 50-year-old woman with metastatic breast cancer and a 63 mm Fuhrman grade 2 clear cell carcinoma. She was treated solely with tamoxifen, a mixed estrogen receptor agonist and antagonist known for its low toxicity and some anti-RCC activity, which previously led to the regression of lung metastases.[27] These observations had established tamoxifen as the standard of care in control groups for clinical trials of immunotherapy.[28] However, due to its low response rate, its use was eventually discontinued.[29] More recently, Mitochondrially targeted tamoxifen (MitoTam) has shown promise, stabilizing disease in four patients and inducing partial responses in one after three lines of therapy.[30] Another patient treated with a combination of bevacizumab, docetaxel, and cisplatin experienced a decrease in diameter by 3.1 mm/year. We hypothesize that tumor shrinkage was mediated by inhibition of the vascular endothelial growth factor pathway by bevacizumab, which has demonstrated meaningful clinical benefits in metastatic RCC in both first- and second-line settings. A randomized phase II trial among cytokine-refractory patients showed a doubling of the time to disease progression compared with the control (4.8 vs. 2.5 months; $P < .001$).[31]

Our findings are consistent with previous studies demonstrating RCC's resistance to chemotherapy. Yet, other agents such as anti-angiogenic agents and tamoxifen may exhibit some activity against RCC. Four patients with hematologic malignancies exhibited stable renal masses. This corroborates the findings of Johnson et al., who reported on six patients with concurrent RCC and hematologic malignancies, noting a 50% 1-year mortality rate, none of which were related to RCC.[32] In any case, the strategy of prioritizing treatment for the other malignancy before addressing the RCC appears to be appropriate.

This study is limited by its retrospective methodology and small sample size. Additionally, despite attempts to meticulously measure cancer diameters, slight deviations could slightly modify the results.

Conclusions

This study evaluated the response of RCC to 29 systemic chemotherapeutic agents, including both traditional and modern agents and several of the most toxic combinations used in hemato-oncology. No solid conclusion regarding any agent can be reached with this methodology. The remarkable resistance of RCC to chemotherapy was confirmed. Nevertheless, the use of tamoxifen, a time-honored and well-tolerated medication, can be reconsidered in combination with modern agents. Similarly, bevacizumab is worth further investigation. This methodology can be adopted in other situations in which there are two clinical conditions, and one takes priority over the other.

Conflict of Interest:

None

Funding:

None

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