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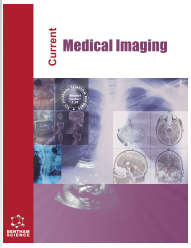

SYSTEMATIC REVIEW

Liesegang Rings in Kidney Diseases- A Systematic Review

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Abstract:

Introduction:

Liesegang rings (LR) are concentric acellular lamellar structures, usually found in cystic and inflammatory tissues but can also be seen in neoplastic conditions. They have been mistakenly interpreted as various structures like psammomatous calcification, parasites, and algae. This study has aimed to systematically review and summarize the existence of LRs in both non-neoplastic and neoplastic conditions of the kidney. The systematic search in PUBMED, PUBMED CENTRAL, and EMBASE along with Google Scholar was performed by using Kidney, Liesegang Rings, or Liesegang structure or pseudo parasitic structure in combination with the Boolean operators ‘’and” as searching terms. Data was collected for demographic characteristics and histopathology diagnosis. The search function was limited to human subjects. Two reviewers independently performed the eligibility assessment and data extraction. Eligibility inclusion criteria were all publications in the English literature worldwide related to Liesegang rings in association with kidney’s non-neoplastic and neoplastic conditions, regardless of the years of publication. Also included were those cases whose full articles were unavailable, but the abstract was well-described, fulfilling our inclusive criteria. Eligibility exclusion criteria included LRs found elsewhere in the body organs apart from the kidney and availability of full text in a different language, non-human, and duplicate article/case.

Methods:

After the exclusion of the articles as per the exclusion criteria, the total articles that fulfilled the inclusive criteria were reviewed. In addition, all the articles were further cross-referenced for additional articles. All published papers retrieved from this search were considered for this review. A total of 22 records (26 cases) were found with a diagnosis of LRs in the kidney to date. Some articles were published as case series. Accordingly, 26 patients were reported to have Liesegang rings associated with kidney neoplastic and non-neoplastic conditions, 12 were male and 14 were female. For one case the gender was not mentioned. LRs presented a higher frequency in individuals between 4th and 5th decades of life. No single case was reported in infants and younger children. Regarding predisposing factors for LRs, cystic fluid contents were the most common underlying condition.

Results:

In our practice, we encountered an unusual case of a 55-year-old female with a complaint of pain in the left upper quadrant of the abdomen. The ultrasound revealed nephrolithiasis and chronic kidney disease for which a nephrectomy was performed. On the histopathological examination, there was an incidental finding of Liesegang rings and a papillary adenoma along with features of chronic pyelonephritis. Our review will provide insight about LRs in different spectrums of kidney diseases.

Conclusion:

This study represents the first available systematic review of the literature demonstrating LRs in the kidney. Although Liesegang rings have no great clinical significance, these, presence in both tissue and cytological specimens should be kept in mind while dealing with different lesions of the kidney as these are good mimickers of many organic and inorganic substances, parasites, and malignancies.

Keywords: Kidney, Adenoma, Pyelonephritis, Parasite, Physiological calcification, Liesegang rings.

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1. INTRODUCTION

Liesegang rings (LR) are rare, benign acellular lamellar structures, which can be seen in myriads of lesions including inflammatory, necrotic, and cystic lesions, and are occasionally found in association with benign and malignant neoplasms. It can be seen at various sites like kidney, breast, conjunctiva, synovium, omentum, pericardium, pleura, maxillary sinus, epididymis, and fallopian tube [1] In the year 1896, the German biochemist, Raphael De. Liesegang described the formation of LR as the Liesegang phenomenon [1, 2]. LRs are formed by periodic precipitation of organic substances from a supersaturated solution within fluid contents of cystic structures [3]. It causes a diagnostic dilemma to the pathologist due to its rare occurrence in routine practice. Herein, we describe all the published cases of Liesegang rings in kidney diseases in indexed English literature.

2. MATERIALS AND METHODS

2.1. Objective

This study aims to review and summarize the existence of LRs in different conditions of the kidney, including non-neoplastic and neoplastic.

2.2. Information Sources and Search Strategy

The systematic computerized search was conducted in PUBMED, PUBMED CENTRAL, and EMBASE databases along with Google Scholar by using the search terms Kidney, Liesegang Rings or Liesegang structure or pseudo parasitic structure in combination with the Boolean operators ‘’and” in the study. Data were collected for demographic characteristics and histopathology diagnosis. The search function was limited to human subjects. The two reviewers carried out the data extraction and eligibility assessment. For Systemic review writing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines was followed.

2.3. Inclusion and Exclusion Criteria

Eligibility inclusion criteria considered all publications over the world, including both histopathology and cytopathology (case reports, case series, letter to editor, and images and comments) related to Liesegang rings in association with kidney non-neoplastic and neoplastic entities, regardless of the year of publication. The exclusion criteria included LRs found elsewhere in the body organs, non-human cases, and duplicate article/cases. After exclusion of the articles as per the exclusion criteria, 19 full-text articles and 3 abstracts were reviewed. In addition, all the articles were further cross-referenced for additional articles. All published papers retrieved from this search were considered for this review (Fig. **1**). As this study is a systematic review of literature, institutional ethical approval is not obtained, and human subjects were not involved in the study directly. We also describe an additional case we encountered in our practice. A 55-year-old female presented to the urology outpatient department complaining of pain in the left upper quadrant of the abdomen for two months. The abdominal ultrasound revealed a shrunken kidney and the presence of renal stones. A left nephrectomy was performed, and the specimen was sent for a histopathology examination. The nephrectomy specimen measured 10cmx9cmx5.5cm, there were multiple cortical scars. On serial slicing, multiple cystic spaces were noted, ranging from 1.5 to 5cm in size, and were filled with pus and black-colored stones (Fig. **2**). The microscopy showed a papillary adenoma, having complex tubulopapillary architecture lined by bland nuclei (Fig. **3A**), numerous globally sclerosed glomeruli, atrophied tubules, and thyroidization of the tubules. The interstitium showed dense lymphocytic inflammation and thick-walled vessels with intimal proliferation. Several spherical laminated ring structures with an amorphous central core surrounded by a double-layer wall were noticed (Fig. **3B**). These were Liesegang rings, which were accentuated on PAS stain, and negative for Von Kossa, Grocott, and Trichrome stains (Fig. **3C**). They are nonpolarizable on polarizing microscopy. These ring-like laminated structures resembled psammoma bodies or parasite ova. The cystic lining showed squamous metaplasia at many places (Fig. **3D**). The diagnosis was rendered as chronic pyelonephritis with nephrolithiasis and coexisting papillary adenoma and Liesegang rings.

3. DISCUSSION

Liesegang rings have been known for centuries, but they are rarely encountered in routine histopathology practices. After a systematic literature search, a total of 22 records (26 cases) were found with a diagnosis of LRs in the kidney to date. LRs presented a higher frequency in individuals between the 4th and 5th decades of life. No single case was reported in infants and younger children. The rings can be identified by their characteristic appearance having a central, amorphous core/nidus; outer, concentric/laminated double-layered appearance; and radial cross-striations. This pattern might result from alternating precipitation and diffusion of supersaturated solutions around a central amorphous nidus. They are usually spherical but can be of various shapes; with a diameter of 5 to 820 μm. It is recognized that the LRs are mistaken with ova, larvae, adult parasites, psammoma bodies, collagenous spherules, globular (spheroid) amyloid, inorganic foreign material such as starch, talc, contrast material, and sometimes with keratin [2]. LR can also be mistaken for cross-sections of *Dioctophyma renale*, the giant kidney worm, expelled by the ureter [4]. The peripheral scalloped pattern and constancy of the size of *D. renale* eggs (60-80 x 39-47 micron) should distinguish them from LR, which is usually not more than 1 mm but show significant variation in size and have a smooth outer ring. Therefore, LR should not be mistaken for cross-sections of the adult worm [5].

The other closest differentials are Michaelis-Gutmann bodies (iron and calcium) and corpora-amylacea (calcium) but are biochemically distinct [6]. Histochemical and immunohistochemical stains for calcium, iron, mucopolysaccharide, amyloid, glycogen, keratin, and epithelial membrane antigen are negative for LR [2]. Psammoma bodies are more basophilic and have calcium when compared with

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LR. Foreign materials lack the specific characteristic of LR, and they are usually birefringent. Tuur *et al*. [7], in a renal cyst aspirate, did an electron probe micro-analysis of LR and demonstrated the emission energy peaks for silicon, calcium, and sulfur. While in contrast, Raso [3] suggested an organic composition and did not show an inorganic element. LRs have been reported in the literature at various sites. However, in this study, only kidney LRs are considered in non-neoplastic [3, 4, 6, 8 - 10, 12 - 16, 18 - 21, 23 - 25] and neoplastic conditions [1, 11, 17, 22] (Table **1**). While doing the literature search it was found that most of the LRs in the kidney are seen in non-neoplastic conditions and mainly renal and perirenal cysts. Shetageri *et al.* [1], Boss *et al.* [11], Vizcaino [17] and Nigdelioglu *et al.* [22], found LRs in association with clear cell Renal cell carcinoma (RCC) and multicystic RCC. However, in the present case, LRs coexisted with papillary adenoma and chronic pyelonephritis. Pegas *et al.* [4] also found LRs in association with xanthogranulomatous pyelonephritis.

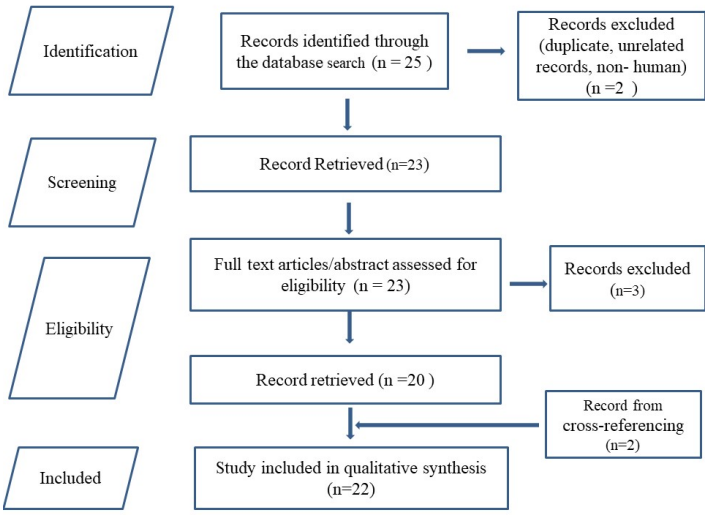

Fig. (1). Flowchart demonstrating the systematic review process of human cases included in this study.

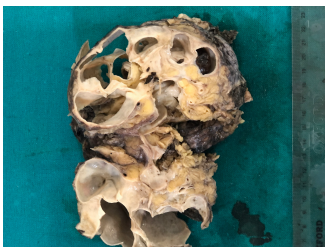

Fig. (2). Gross view of the nephrectomy specimen showing multiple cystic spaces.

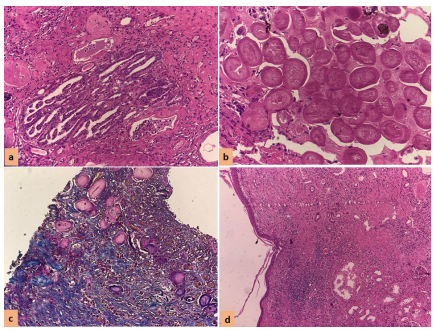

Fig. (3). Photomicrographs of the kidney. **A** - Papillary Adenoma showing complex tubulopapillary architecture lined by bland nuclei. (H & E, 200x); **B** - Spherical laminated rings with double layer wall (H & E, 400x); Masson Trichrome negative rings (200x); **D** - Cyst lining showing squamous metaplasia (H & E,100x).

Table 1. Liesegang rings reported with various non-neoplastic and neoplastic renal entities.

-	Year	Author	Age/Sex	Clinical Condition
1	1988	Sneige [10]	48/M 60/M	Perirenal Hemorrhagic cyst
2	1988	Sneige [9]	39/M 60/M	Renal/Perirenal hemorrhagic cysts
3	1989	Boss [11]	66/F	Multicystic RCC
4	1990	Laurie [8]	52/F 61/F 79/F	3 cases of Renal cyst fluid
5	1992	Krueger [12]	81/M	Renal hemorrhagic cyst
6	1996	Zámecník [13]	28/F	Dilated Renal Calyx
7	1997	Glazier [14]	59/F	Perirenal cyst
8	1998	Raso [3]	64/F	Renal Cyst
9	1999	Todd [15]	NM	Renal cyst
10	1999	Kim [24]	59/M	Renal hemorrhagic cyst from the donor kidney
11	2004	Missselevich [16]	43/F	Hemorrhagic Urine
12	2005	Vizcaino [17]	64/F	Pseudotumor of renal pelvis
13	2005	Yusuf [18]	63/M	Perirenal Cyst
14	2006	Shum [19]	35/M	Renal Cyst
15	2006	Chikkamuniyapa [6]	67/M	Multiple benign renal cyst
16	2010	Pegas [4]	51/F	Xanthogranulomatous pyelonephritis
17	2013	Wood [20]	68/M	Renal cyst mimicking RCC
18	2013	Bhat [21]	57/M	Simple renal cyst
19	2018	Nigdelioglu [22]	66/F	Pseudo fungi in a cystic renal cell carcinoma
20	2019	Shetageri [1]	40/F	Clear cell renal cell carcinoma
21	2019	Bavi [23]	76/M	Renal cyst and pancreatic adenocarcinoma
22	2022	Gross [25]	59/F	Diabetic nephropathy
	2022	*Present Case*	*55/F*	*Chronic pyelonephritis with papillary adenoma*

Note: NM= non mentioned.

Wood *et al.* [20] noted LRs in a cystic renal lesion that mimicked RCC, and it was due to the formation of a well-circumscribed mass of hemosiderin-laden macrophages and LRs around the ruptured cyst. They diagnosed this after a urinary tract infection that was a post-operative complication of total hip replacement surgery. Hence, they concluded that this type of renal pseudotumor should be considered while listing the differential diagnoses of the renal masses. Similarly, Vizcaino *et al.* [17], also reported a solid pseudotumor of renal pelvis, which was nothing but xanthogranulomatous inflammation with LRs. Misselevich *et al.* [16] found LRs in hemorrhagic urine, which was a unique finding for them as most of the reported cases in literature had reported LRs in the tissue. Most of the cases were females, including the present case, and are above 40 years of age. The common features found among these cases were cystic structure in both neoplastic and non-neoplastic entities. The LRs are thought to arise through the Liesegang phenomenon, where the formation of ring-like structures occurs when two colloids are diffusing into one another to form alternating zones of hyper- and hypo-saturation. It was proposed that the nucleating particle decrease the rate of nucleation and enhance the precipitation in areas of supersaturation and sub saturation [**3**]. The nidi can be microorganisms or foreign bodies in the formation of LRS. In nature, this phenomenon is proposed to be followed by calcium carbonate in oolitic limestone, coloration pattern of butterfly wings. The high-molecular-weight polymers if present in the inflamed and cystic tissue may produce a colloidal extracellular environment like that of the colloidal gels in which LRs are formed *in vitro* [**7**]. The morphology is better appreciated in cytological preparations rather than in paraffin-embedded sections, as histologic processing may produce artifacts [8]. The LRs have been reported in both fluids as well as tissue at extra and intracellular sites. Nigdelioglu *et al.* [22] detected LRs along with pseudo fungi incidentally in the fluid aspirated from the cystic RCC and hence they concluded that awareness of the occurrence of these structures in FNAs of cystic lesions, including cystic neoplasm, can prevent potential diagnostic pitfalls. Todd *et al.* [15] did a cytological study of 41 different cystic lesions of kidneys and found only one case with LRs in a simple renal cyst. The electron microscopy revealed electron-dense amorphous core and fibrillary lucent concentric circles [9]. X-ray diffraction did not reveal any significant energy peaks or diffraction patterns at a variety of spot sizes in LRs. The X-ray diffraction, histochemical and immunohistological investigations were unable to clarify their nature [3]. Bhavi *et al.* [23] had reported a case of milk of renal calcium cyst with Liesegang structures in an autopsy, done on a patient who received neoadjuvant chemotherapy and was enrolled in a clinical trial involving irreversible electroporation (IRE) for pancreatic carcinoma. The report highlights the relationship between “milk of calcium cysts” in radiology, and “Liesegang rings” in pathology. They found that this was the first report of such structures in a patient who received IRE therapy. The

study shows some facts that Liesegang rings are uncommon findings and have no great clinical significance. Commonly seen in 4th and 5th decades of life, with slight female preponderance. LRs are seen in the cystic fluid contents or hemorrhagic or necrotic tissue of both non-neoplastic and neoplastic lesions of the kidney. These are great mimicker of many organic, inorganic substances along with parasites and sometimes with malignancy. The limitation of the study includes a smaller number of cases reported in association with kidney conditions.

CONCLUSION

Liesegang rings are uncommon pathological findings, but they may cause diagnostic dilemmas to pathologists. Hence, awareness is necessary for the pathologist to prevent misinterpretation and overdiagnosis as parasites or even malignancy and other mimickers. This review would help young and emerging pathologists and clinicians to understand this entity better and avoid unnecessary treatments.

LIST OF ABBREVIATIONS

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses

LR = Liesegang rings

RCC = Renal cell carcinoma

IRE = Irreversible electroporation

AUTHORS CONTRIBUTION

-	**Jyotsna Naresh Bharti**	**Sushma Bharti**	**Jitendra Singh Nigam**
Planning	✓	✓	✓
Conduct	✓	✓	✓
Reporting	✓		
Concepts & Design	✓	✓	✓
Data acquisition	✓	✓	✓
Data Interpretation	✓	✓	✓
Manuscript preparation, editing & review	✓	✓	✓

CONSENT FOR PUBLICATION

Patient Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for their images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal their identity, but even though anonymity cannot be guaranteed.

AVAIALABILITY OF DATA AND MATERIALS

All the data and supportive information are provided within the article.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

FUNDING

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CONFLICT OF INTEREST

The authors declared no conflict of interest financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

Supplementary material is available on the publisher's website along with the published article.

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