Warfarin-related nephropathy

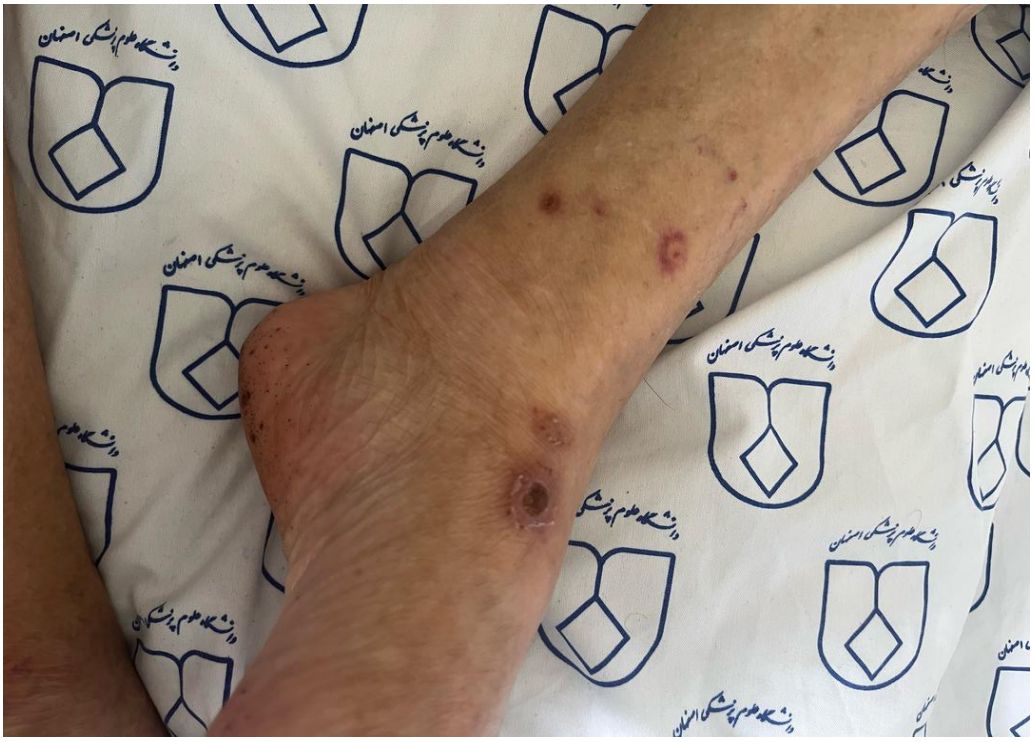
Mojgan Mortazavi

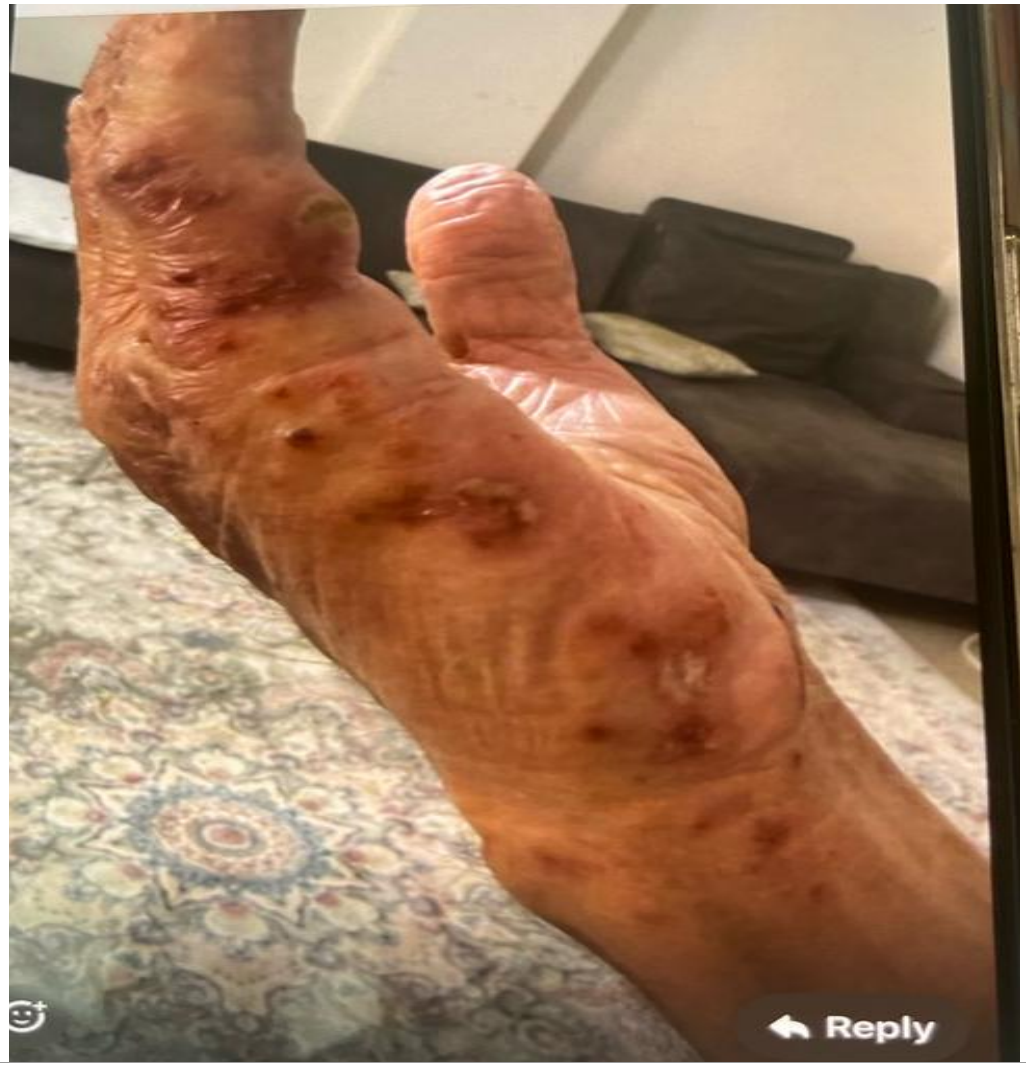
Professor of nephrology

Isfahan Kidney Diseases Research Cen

Case present

- 80 years old man came with AKI /bloody urine and skin involvement (rash with sever pruritus and target lesion in his hands and legs)
- BUN=40mg/dl
- Cr=2.8 mg./dl
- U/A: Gross hematuria/ Pr=3+ /RBC=many


دانشگاه علوم پزشکی اصفهان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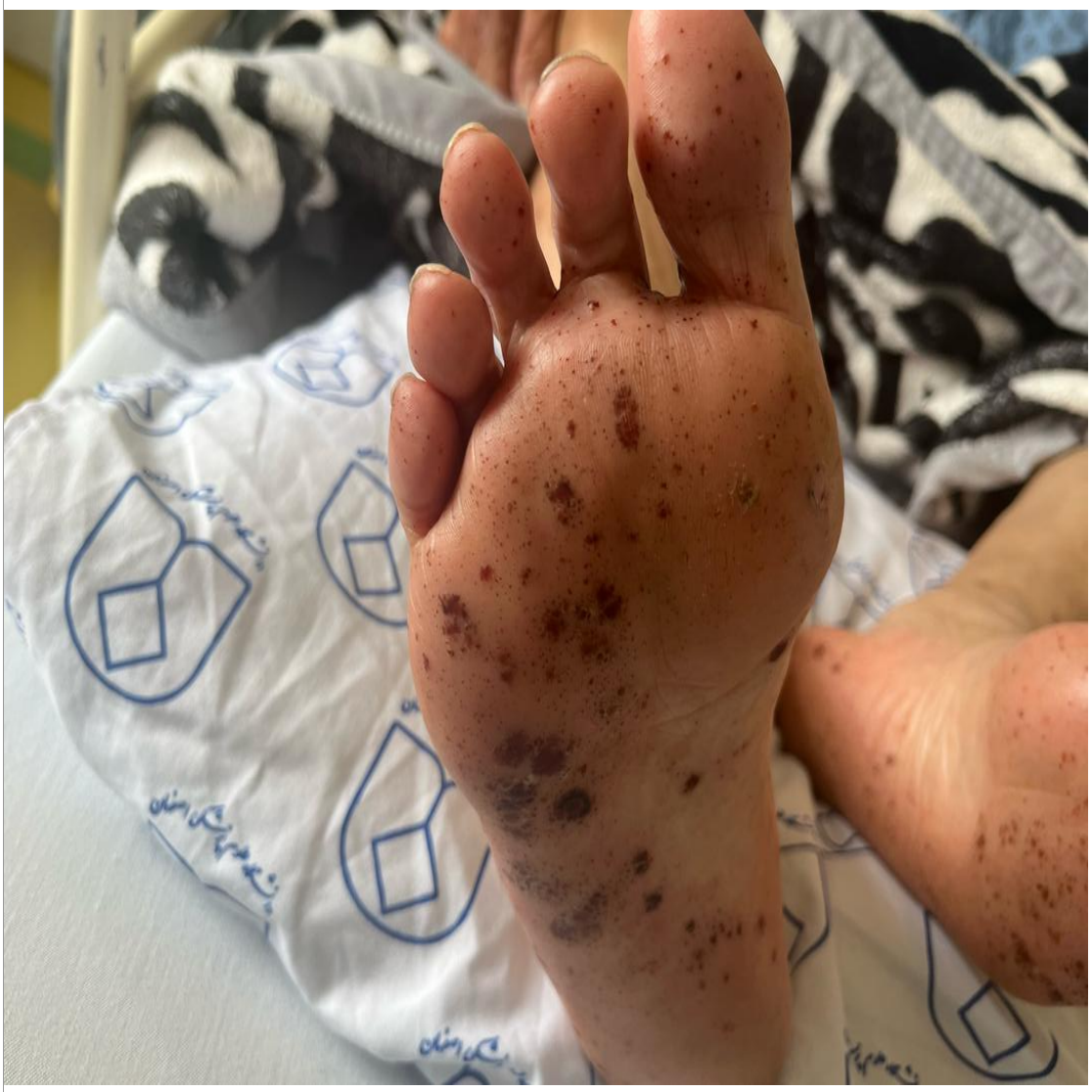


Digital Panoramic, Cephalometric & Periapical Radiography رادیولوژی دندانی دیجیتال

نام بیمار : آقای عباسعلی امینی سن : ۸۱ سال تاریخ : ۱۴۰۴/۰۱/۳۰

همکار گرامی.

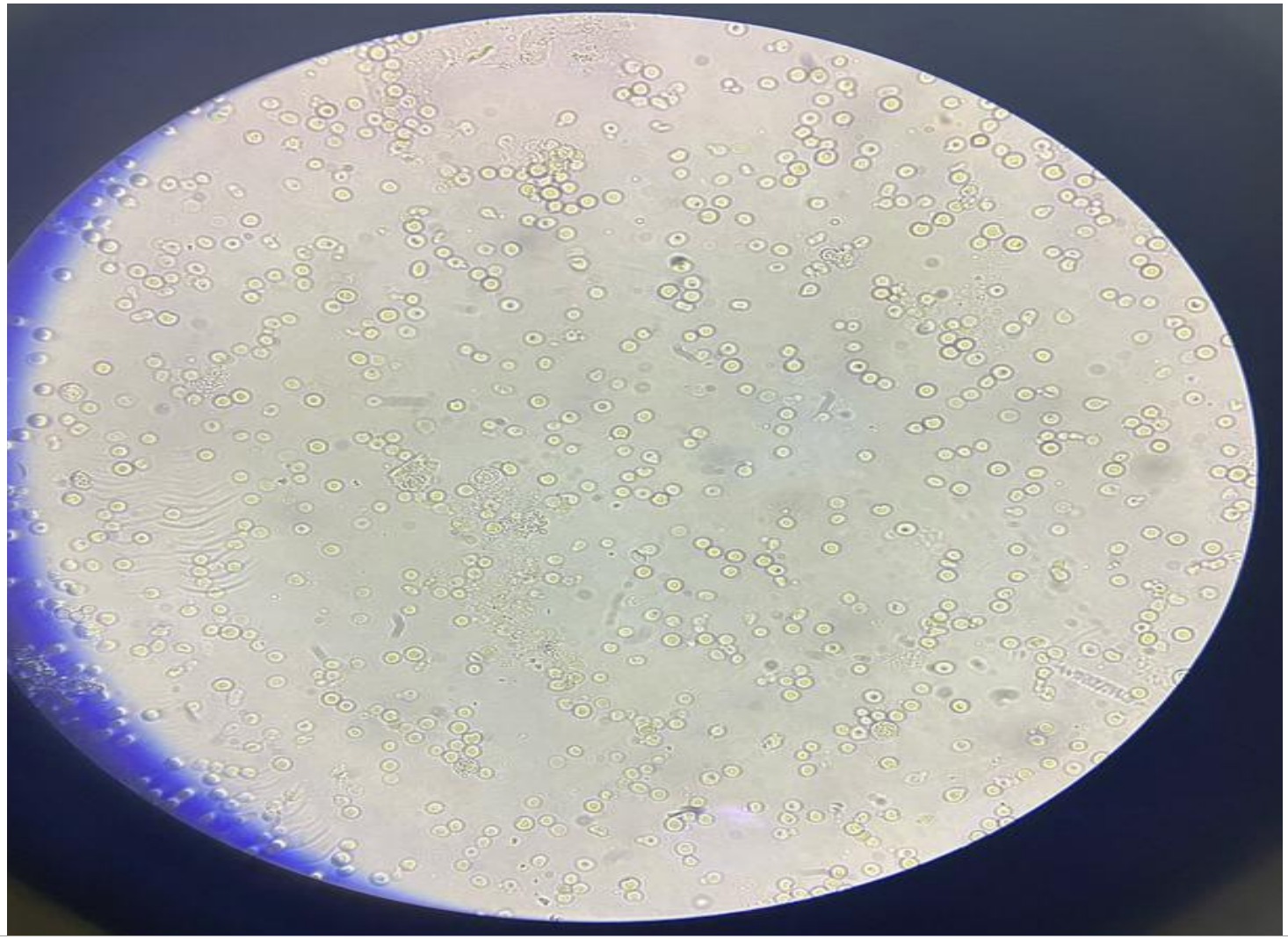
با سلام و عرض ادب :

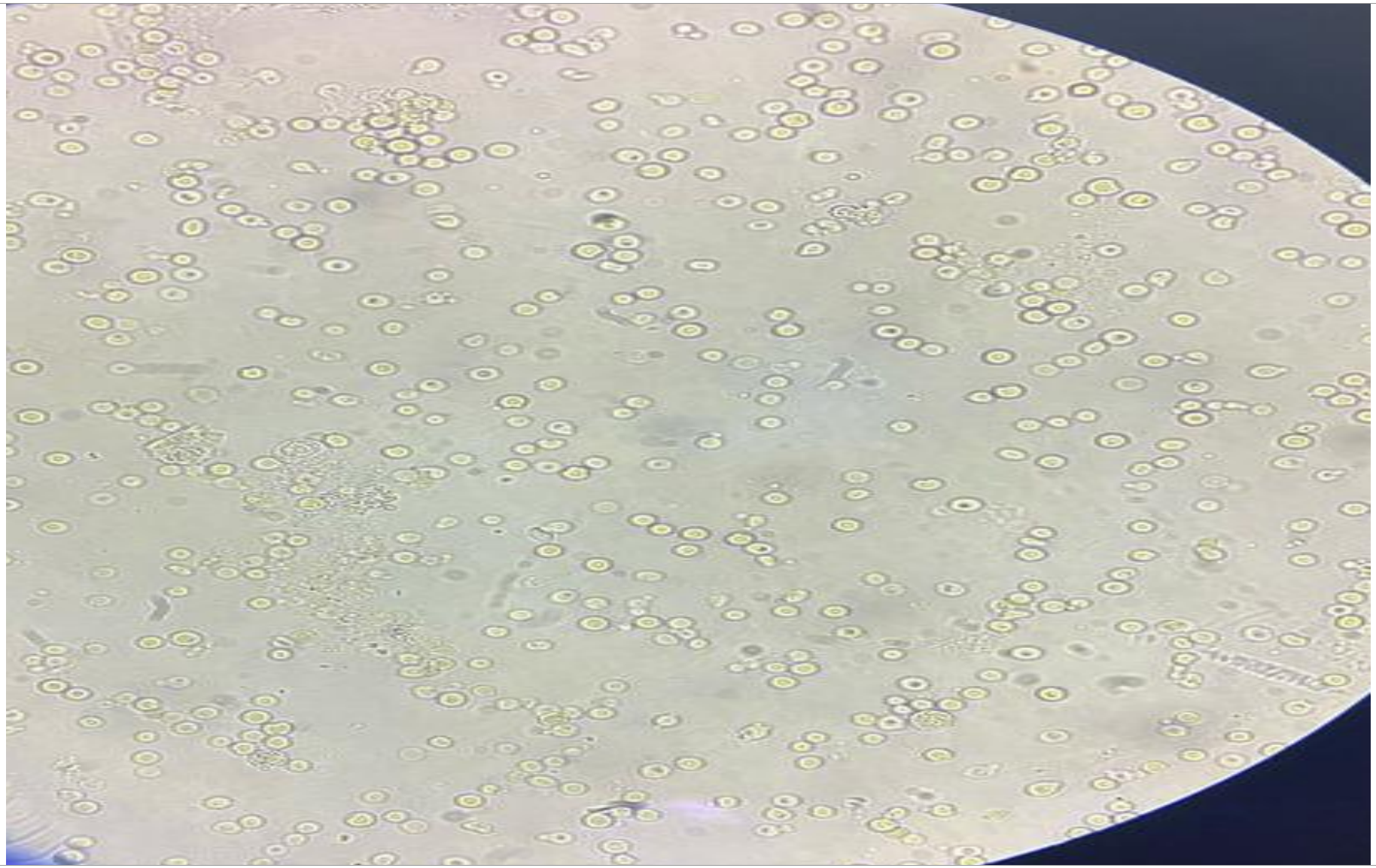
سونوگرافی کامل شکم و لگن و رتروپریتوئن :

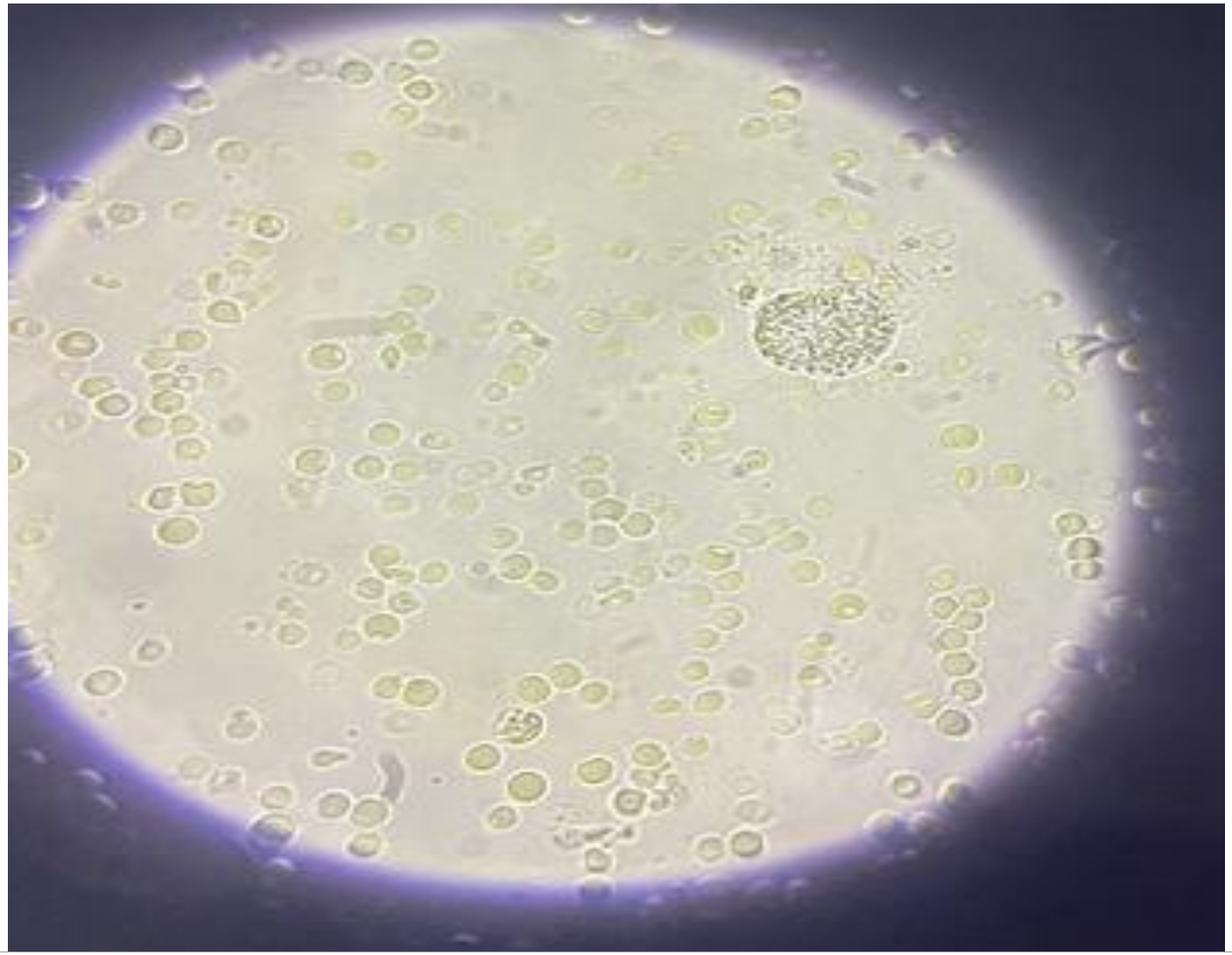
کبد دارای ابعاد و اکوی طبیعی است و ضایعه کیستیک و یا solid در آن مشهود نمی باشد.(Span:127 mm)
اتساع در مجاری صفراوی داخل و خارج کبدی مشهود نمی باشد.
قطر عروق PORT و ورید های کبدی طبیعی می باشد.
کیسه صفرا دارای حجم و ضخامت جدار طبیعی بوده و فاقد سنگ صفراوی می باشد.
ابعاد طحال برابر با ۹۲*۴۰ میلیمتر و اکوی پارانشیمال آن هموژن است.
قسمت های مشاهده شده پانکراس دارای نمای طبیعی می باشند.
طول کلیه راست برابر با ۱۱۸ میلیمتر و ضخامت پارانشیمال آن ۱۵ میلیمتر می باشد.
طول کلیه چپ برابر با ۱۱۵ میلیمتر و ضخامت پارانشیمال آن ۱۵ میلیمتر می باشد.
اکوژنیسیته پارانشیم کلیه ها مختصرا افزایش یافته می باشد.
یک کیست کورتیکال ساده به قطر ۶ میلیمتر در پل تحتانی کلیه راست مشاهده می شود.
یک کیست کورتیکال ساده به قطر ۲۱ میلیمتر در پل میانی کلیه چپ مشاهده می شود.
سنگ و هیدرونفروز در کلیه ها مشهود نمی باشد.
انتهای پروگزیمال و دیستال حالبها متسع نبود.
ضخامت جدار مثانه طبیعی بوده و فاقد سنگ و ضایعه فضاگیر می باشد.
fine trabeculation در جدار مثانه مشهود است.
پروستات دارای ابعاد ۴۹*۵۱*۵۱ میلیمتر و حجم ۶۷ سی سی بزرگتر از حد نرمال می باشد و به کف مثانه برجستگی دارد.
مایع آزاد در شکم و لگن مشهود نیست.

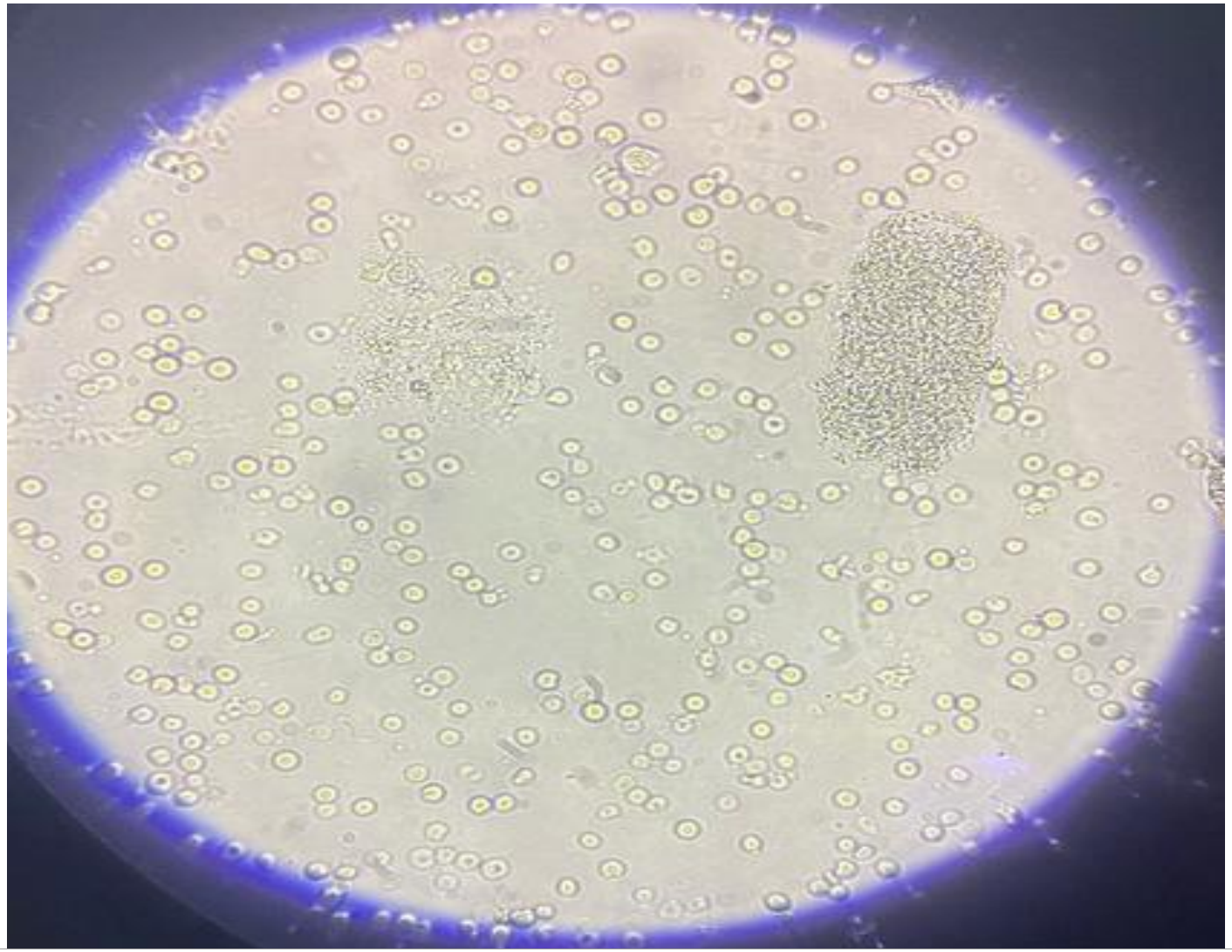
دکتر جواد ونسرخی
متخصص رادیولوژی و سونوگرافی
CT اسکن
نظام پزشکی

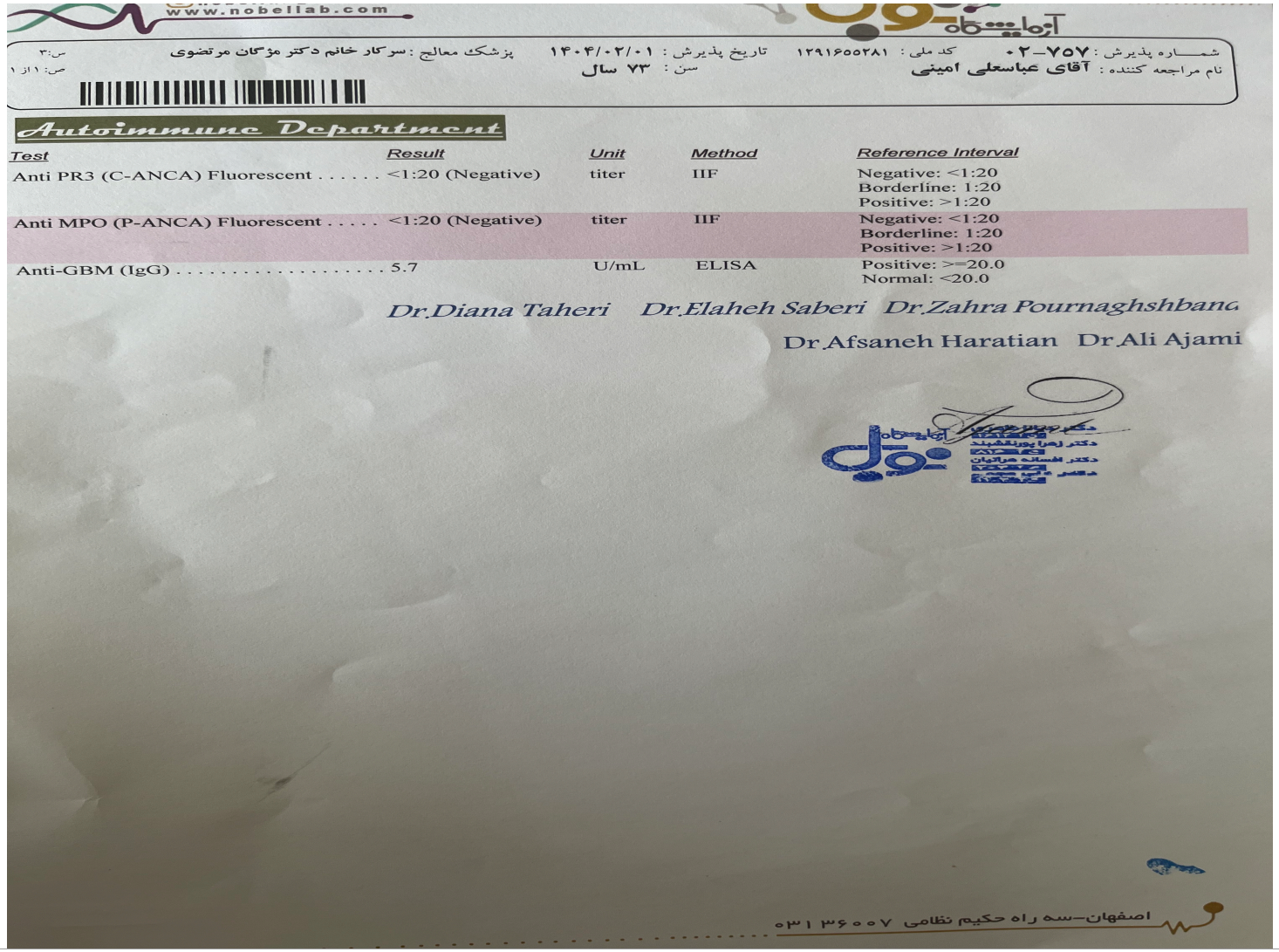
درس : اصفهان، خیابان سروش، حد فاصل فلکه احمد آباد و چهار راه آل خجند، کوچه شماره ۱۷، دشت گل تلفن : ۲۹۸۵۳۳











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آزمایشگاه نوبل

شماره پذیرش : ۰۲-۷۵۷ کد ملی : ۱۲۹۱۶۵۵۲۸۱ تاریخ پذیرش : ۱۴۰۴/۰۲/۰۱ پزشک معالج : سرکار خانم دکتر مژگان مرتضوی
نام مراجعه کننده : آقای عباسعلی امینی سن : ۷۳ سال
ص: ۱ از ۱ س: ۳

Autoimmune Department

Test	Result	Unit	Method	Reference Interval
Anti PR3 (C-ANCA) Fluorescent	<1:20 (Negative)	titer	IIF	Negative: <1:20 Borderline: 1:20 Positive: >1:20
Anti MPO (P-ANCA) Fluorescent	<1:20 (Negative)	titer	IIF	Negative: <1:20 Borderline: 1:20 Positive: >1:20
Anti-GBM (IgG)	5.7	U/mL	ELISA	Positive: >=20.0 Normal: <20.0

Dr.Diana Taheri Dr.Elaheh Saberi Dr.Zahra Pournaghshband
Dr.Afsaneh Haratian Dr.Ali Ajami

اصفهان-سه راه حکیم نظامی ۰۳۱۳۶۰۰۷

مرکز آموزشی و درمانی الزهرا(س)

جوابدهی سونوگرافی

نام و نام خانوادگی بیمار	عباسعلی امینی رارانی	کدپذیرش بیمار	۹۳۷۹۶۱
پزشک برگه	حاجی هاشمی - علی		
کد برگه	۷۷,۲۴۰	بیمه بیمار	آزاد
سن	80		

بخش	جراحی منتخب یک۶۲۱۳-۶۲۱۴		
تاریخ برگه	۱۴۰۴/۰۱/۳۱ ۰۹:۱۱		

نام خدمت: سونوگرافی کلیه ها و مجاری ادراری(شامل مثانه پر)

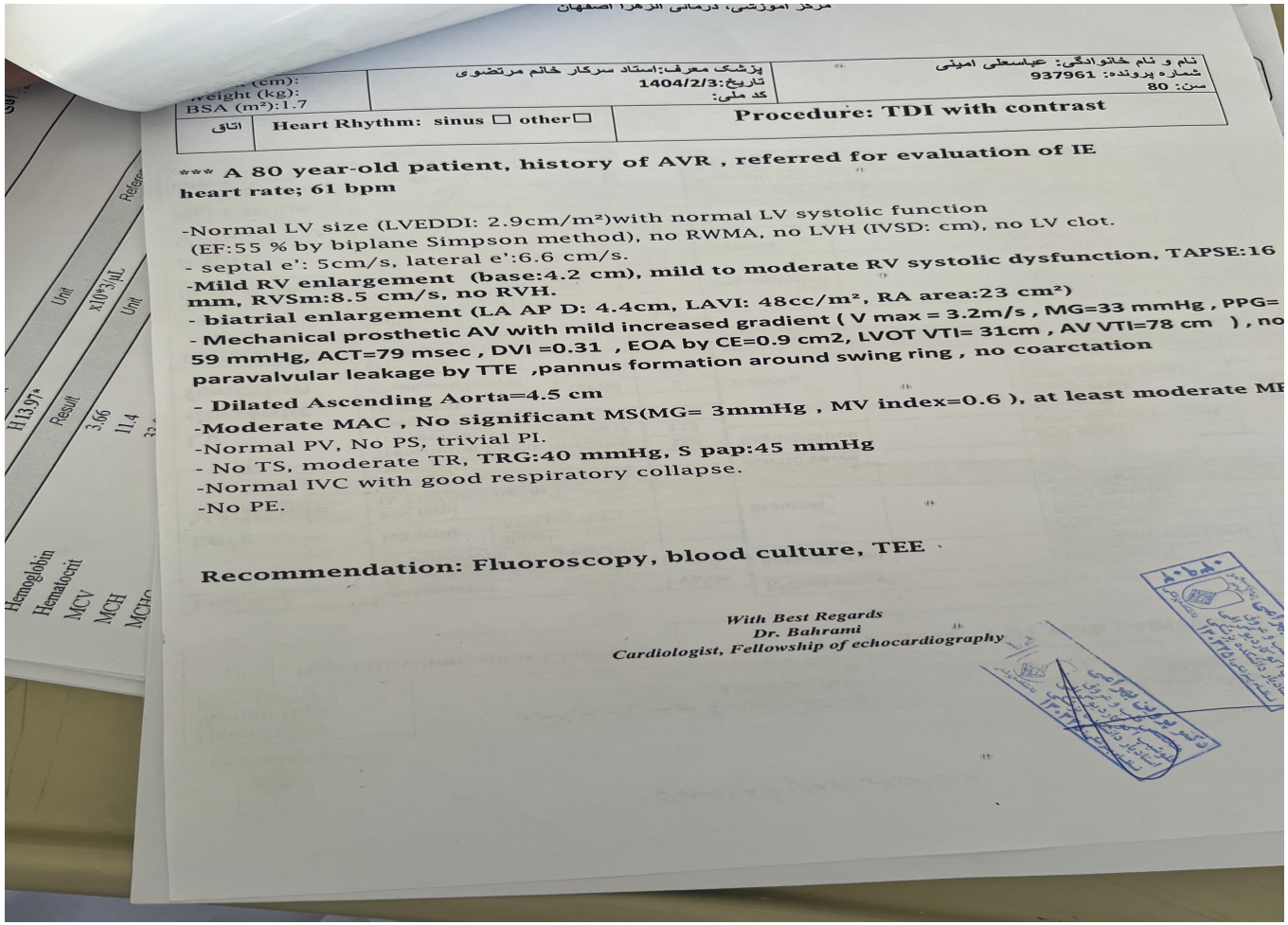
هر دو کلیه دارای شکل و ابعاد و ضخامت پارانشیمال نرمال است .اکوی پارانشیمال کلیه ها افزایش یافته لذا چک BUN/Cr توصیه می شود .
کلیه راست به طول ۱۰۷میلیمتر و ضخامت پارانشیمال ۱۵میلیمتر
کلیه چپ به طول۱۰۵ میلیمتر و ضخامت پارانشیمال ۱۳میلیمتر
تصویر یک کیست کورتیکال واجد thin septa به دیامتر ۲۰ م.م در پل میانی کلیه چپ رویت شد.
تصویر سنگ به دیامتر ۵ م.م در کالیس تحتانی کلیه راست مشهود است.
هیدرونفروز در کلیه ها رویت نشد .
مثانه نیمه پر و دارای حجم و ضخامت جداری نرمال می باشد .
روستات به ابعاد ۴۲*۴۶*۵۱ م.م و به حجم تقریبی ۶۳ سی سی افزایش یافته رویت شد.
ریدنت سال ۱: دکتر عمادیان
ریدنت سال ۲: دکتر جوکاری
ریدنت سال ۳: دکتر جعفری

نام دستیار: - - -

نام پزشک: حاجی هاشمی - علی

دکتر علی حاجی هاشمی
متخصص رادیولوژی
نظام پزشکی ۱۷۸۶۲۷

۱۴۰۴/۰۱/۳۱ ۱۱:۰۹



مرکز آموزشی، درمانی الزهرا اصفهان

...(cm): ...eight (kg): BSA (m^2):1.7	پزشک معرف:استاد سرکار خانم مرتضوی تاریخ:1404/2/3 کد ملی:	نام و نام خانوادگی: عباسعلی امینی شماره پرونده: 937961 سن: 80
اتاق	Heart Rhythm: sinus ☐ other☐	Procedure: TDI with contrast

***** A 80 year-old patient, history of AVR , referred for evaluation of IE**
heart rate; 61 bpm

-Normal LV size (LVEDDI: 2.9cm/m^2)with normal LV systolic function
(EF:55 % by biplane Simpson method), no RWMA, no LVH (IVSD: cm), no LV clot.
- septal e': 5cm/s, lateral e':6.6 cm/s.
-Mild RV enlargement (base:4.2 cm), mild to moderate RV systolic dysfunction, TAPSE:16 mm, RVSm:8.5 cm/s, no RVH.
- biatrial enlargement (LA AP D: 4.4cm, LAVI: 48cc/m^2, RA area:23 cm^2)
- Mechanical prosthetic AV with mild increased gradient (V max = 3.2m/s , MG=33 mmHg , PPG= 59 mmHg, ACT=79 msec , DVI =0.31 , EOA by CE=0.9 cm2, LVOT VTI= 31cm , AV VTI=78 cm) , no paravalvular leakage by TTE ,pannus formation around swing ring , no coarctation

- Dilated Ascending Aorta=4.5 cm
-Moderate MAC , No significant MS(MG= 3mmHg , MV index=0.6), at least moderate MR
-Normal PV, No PS, trivial PI.
- No TS, moderate TR, **TRG:40 mmHg, S pap:45 mmHg**
-Normal IVC with good respiratory collapse.
-No PE.

Recommendation: Fluoroscopy, blood culture, TEE

With Best Regards
Dr. Bahrami
Cardiologist, Fellowship of echocardiography

Clinical and Experimental Medicine (2024) 24:148
https://doi.org/10.1007/s10238-024-01412-1

CASE REPORT

Warfarin-related nephropathy: unveiling the hidden dangers of anticoagulation

Fengbo Xu[1] · Guoqin Wang[1] · Lijun Sun[1] · Hong Cheng[1]

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Abstract

Warfarin-related nephropathy (WRN) is defined as acute kidney injury subsequent to excessive anticoagulation with warfarin. Patients with mechanical prosthetic valves require long-term anticoagulant therapy. Nonetheless, warfarin remains the sole available option for anticoagulant therapy. Consequently, patients with mechanical prosthetic valves constitute a special group among the entire anticoagulant population. The present study recorded two cases of patients who had undergone mechanical prosthetic valve surgery and were receiving warfarin therapy. They presented to the hospital with gross hematuria and progressive creatinine levels. Notably, their international normalized ratio (INR) did not exceed three. Subsequent renal biopsies confirmed WRN with IgA nephropathy. The two patients continued to receive warfarin as anticoagulation therapy and were prescribed oral corticosteroids and cyclophosphamide, which resulted in improved renal function during the follow-up. Based on a review of all relevant literature and the present study, we proposed a new challenge: must elevated INR levels be one of the criteria for clinical diagnosis of WRN? Perhaps some inspiration can be drawn from the present article.

Keywords Warfarin-related nephropathy · Acute kidney injury · International normalized ratio · IgA nephropathy

Warfarin-related nephropathy (WRN)
unveiling the hidden dangers of anticoagulation

- Warfarin-related nephropathy (WRN) is **an increasingly recognized disease, mainly associated with excessive anti- coagulation with warfarin.**
- WRN is defined as the manifestation of acute kidney injury (AKI) within a week after the interna- tional normalized ratio (INR) exceeds **3**
- Despite the development of direct oral anticoagulants (DOACs), research findings on the efficacy of DOACs in preventing valve thrombosis in patients with artificial valves have been inconsistent
- Therefore, warfarin remains the only available option for anticoagulants in this population.

Mechanism underlying AKI in WRN

- The primary mechanism underlying AKI in WRN is the occurrence of **glomerular hemorrhage** and **tubular obstruction** caused by RBC casts.
- The pharmacokinetics of warfarin are influenced by various drugs and foods, and there is a potential risk of excessive warfarinization during long-term use.
- Patients with mechanical artificial valves have a high risk of “valve blockage” if warfarin is discontinued, which in turn limits the number of patients who can undergo renal biopsy when WRN is suspected in clinical practice.
- Consequently, there are currently no alternative oral anticoagulants to substitute warfarin.

Mechanism underlying AKI in WRN

- According to the findings in previous literature, except for **IgA nephropathy**, WRN frequently coexists with:
- **diabetic nephropathy**,
- **lupus nephritis**,
- **thin basement membrane nephropathy**,
- and **other glomerular diseases** .
- .

Mechanism underlying AKI in WRN

- It is widely recognized that warfarin can decrease thrombin levels by inhibiting prothrombin synthesis.
- Thrombin, in turn, can bind and activate a family of proteinase-activated receptors (PARs) that are expressed in numerous cells, including glomerular endothelial cells.
- It is hypothesized that activation of PARs provides trophic support to maintain endothelial integrity.
- Consequently, the decrease in thrombin levels induced by warfarin breaks down the endothelial barrier, thereby facilitating glomerular hemorrhage .

Mechanism underlying AKI in WRN

- Patients with chronic kidney disease (CKD) of multiple etiologies frequently have a pathological foundation of glomerular endothelial injury, thereby significantly increasing the probability of WRN.
- Meanwhile, studies found that the transcription and concentration of cytochrome P450 enzymes were lower in CKD animal models, resulting in reduced drug metabolism and an increased risk of overdose .
- This may also contribute to the heightened susceptibility of CKD patients to WRN.

Treatment of WRN

- **Currently, there is a lack of established guidelines for treating WRN**.
- The predominant strategies address coagulopathy and offer comprehensive supportive care.
- **Early administration of steroids** has been reported to accelerate recovery from the classic inflammation observed in drug (anticoagulant)-induced nephritis .
- Other studies have indicated that the etiopathogenesis of tubular injury associated with RBC casts can be ascribed to the detrimental local effects of catalytic **iron** released from decaying erythrocytes.
- The latter is thought to stimulate excessive production of **hydroxyl radicals**, damaging the lipoprotein components of tubular cell membranes and ultimately leading to **apoptosis/necrosis of the tubular cells** .

Treatment of WRN

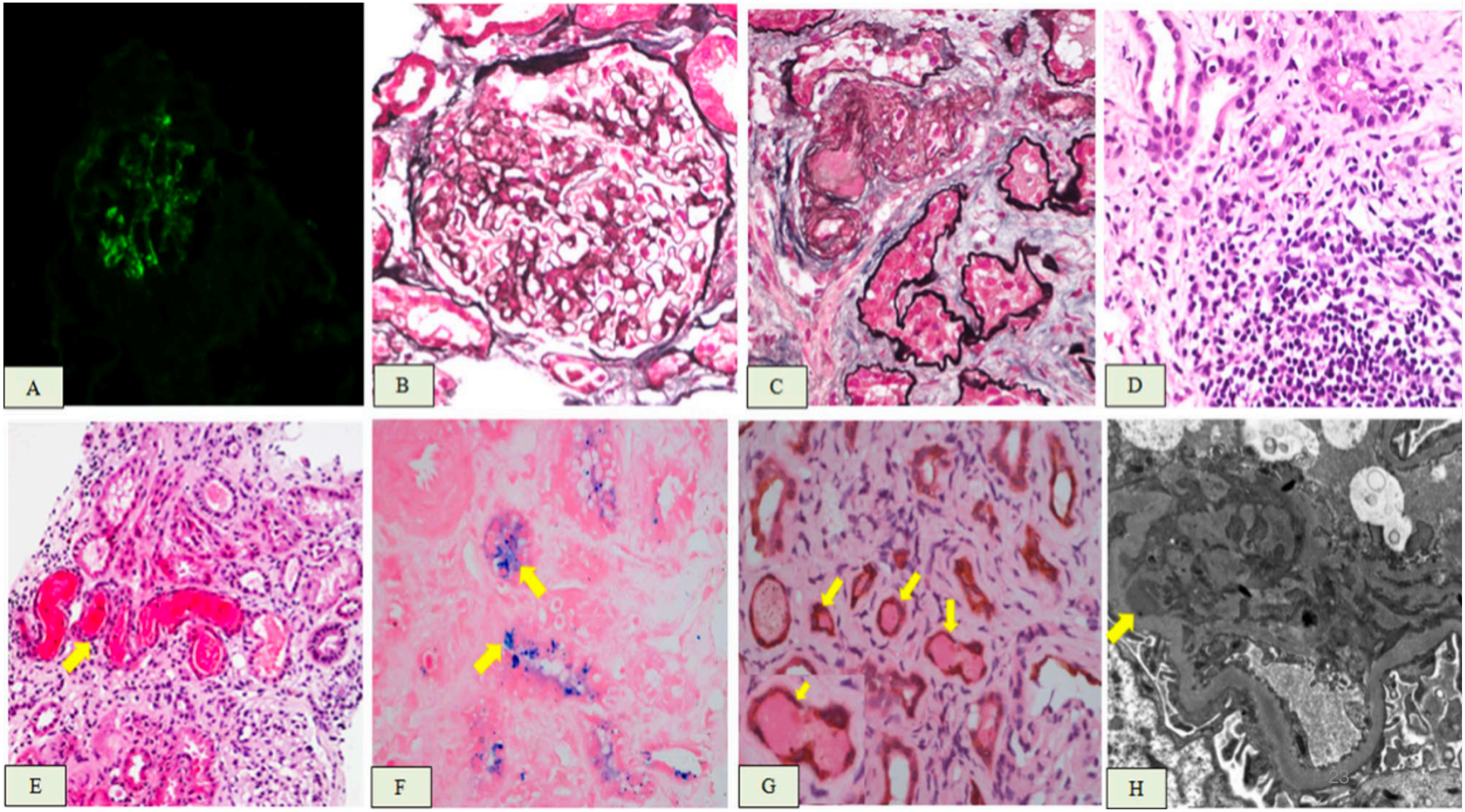
- Studies have demonstrated that corticosteroids can ameliorate associated tubulointerstitial injury and prevent progression to irreversible fibrosis.
- Theoretically, **glucocorticoids** may be a viable option for WRN therapy.
- Certain scholars have also highlighted that glucocorticoids are commonly used in anticoagulant-related nephropathy patients with potential IgA nephropathy and in patients with more prominent crescent lesions or tubulointerstitial inflammation.
- Such treatment aims to alleviate inflammatory responses and promote renal recovery .

Table 1 Clinical and demographic data of WRN patients with prosthetic valves

Patient no.	Country of author	Age (*y*)	Sex	Symptoms	Time to ARN onset	Surgery	INR (IU)	Baseline Scr (μmol/L)	Scr at Biopsy (μmol/L)	Renal biopsy pathology	Medications	Outcome
1 [7]	Slovenia	51	*M*	Gross hematuria	15 years	Aortic valve replacement	5.0	170–200	249	IgAN, ATI	Temporary stop warfarin; steroids	Incomplete recovery
2 [7]	Slovenia	76	*M*	Gross hematuria	10 years	Aortic valve replacement	4.4	430	487	global glomerular sclerosis, ATI	Dialysis; better control of INR	Dialysis
3 [7]	Slovenia	56	*F*	Microscopic hematuria	11 months	Aortic valve replacement	2.42	72	81	IgAN	Better control of INR	Stable kidney function
4 [7]	Slovenia	66	*M*	Gross hematuria	26 years	Aortic valve replacement	1.36	149	669	IgAN	Transiently converted to heparin	Kidney function slightly improved
5 [8]	Singapore	56	*F*	Microscopic hematuria	6 years	Valve replacement	4.95	72	317	IgAN	Prednisolone; acetylcysteine;	Incomplete recovery
6 [9]	India	50	*F*	Gross hematuria	2 years	Mitral valve replacement	4.70	80	415	acute tubulointerstitial nephritis	Steroids; temporary stop warfarin	Complete recovery
7 [10]	USA	57	*F*	Gross hematuria	26 years	Aortic valve replacement	3.71	274	518	diffuse mesangial proliferative glomerulonephritis ATI	Steroids; dialysis	Dialysis
8 [11]	Japan	55	*M*	Gross hematuria	13 years	Aortic valve replacement	3.75	67	796	IgAN	Supportive care	Incomplete recovery
9 [12]	Tailand	56	*M*	Gross hematuria	2 years	Aortic valve replacement	6.08	124	1017	ATI	Temporary stop warfarin; oral vitamin K; dialysis	Incomplete recovery
10 [13]	USA	61	*M*	Gross hematuria	available	Mitral valve replacement	3.52	180	601	IgAN	Steroids; dialysis	Dialysis
11*	China	56	*F*	Gross hematuria	9 months	Aortic valve replacement	2.08	121	215	IgAN, ATI	Steroids; cyclophosphamide	Incomplete recovery
12*	China	63	*F*	Gross hematuria	5.5 years	Aortic valve replacement	2.69	170	219	IgAN, ATI	Steroids; cyclophosphamide	Incomplete recovery

SCr, serum creatinine; *INR*, international normalized ratio; *RBC*, red blood cell; *IgAN*, IgA nephropathy; *LMWH*, low molecular weight heparin; *ATI*, acute tubular injury

*The present study


A
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WCN24-2271

WARFARINRELATED NEPHROPATHY IN TWO PATIENTS WITH MECHANICAL VALVES

Hong Cheng*[1], Fengbo Xu[2], Guoqin Wang[2], Lijun Sun[2], Yanyan Wang[2], Lingqiang Kong[2]

[1]Beijing, Renal Division, China, [2]Renal Division, Beijing Anzhen Hospital, Capital Medical University, Beijing

Introduction: Warfarin-related nephropathy (WRN) is defined as acute kidney injury subsequent to excessive anticoagulation with warfarin. Patients with mechanical valves required long-term anticoagulant therapy, and warfarin remains the sole available option for anticoagulant therapy. Consequently, patients with mechanical valves constitute a special group among the entire anticoagulant population. The present study recorded two patients receiving warfarin therapy for mechanical valve presented to the hospital with gross hematuria and progressive creatinine levels.

Methods:

Results: **Case Description:** The first patient was a 56-year-old female, who had previously undergone mechanical aortic valve replacement surgery nine months ago and was prescribed warfarin, was admitted to the hospital due to the occurrence of gross hematuria six days before hospitalization. Additionally, her creatinine levels exhibited a rapid increase from 120.5umol/L to 207.5µmol/L within three days.Laboratory analysis revealed a creatinine level of 167.8 µmol/L,albumin level of 39.6g/L, and an INR value of 2.08.The urinary test results indicated the presence of urinary protein(+) and urinary occult blood(3+).The quantification of urinary protein over a 24-hour period was measured at 0.69g.The immunoglobulin,complements, ANA, ANCA, anti-GBM antibody, serum protein electrophoresis,serum light chains and PLAR2 were within normal range.The second patient was a 63-year-old male,who has been diagnosed with hypertension for the twenty years, underwent Bentall+Sun's surgery for type A aortic dissection five years ago. Following the surgery, the patient was prescribed warfarin. The patient was admitted to the hospital due to persistent gross hematuria for a duration of twenty days and an increase in creatinine levels.Upon admission, laboratory analysis revealed a creatinine level of 169.9µmol/L (which was within the normal range one year ago), and an INR of 2.69.The urinary test indicated the presence of urinary protein (2+) and urinary occult blood (3+).Urinary protein quantification was 3.06g/24 hours. The serum IgA level was measured at 4.55g/L (normal range:1.0-

WCN24-2472

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE AMONG ENDSTAGE RENAL DISEASE PATIENTS IN KATHMANDU, NEPAL

Shailendra Sharma*[1], Sweta Koirala[2], Yoko Inagaki[3], Rishi Kumar Kafle[4], Sweta Koirala[2], Nasatya Khadka[2], Pooja K.C[5], Kristina Margareta Jakobsson[6], Jason R. Glaser[7], Dinesh Neupane[8]

[1]Okemos, MI, Nephrology, United States; [2]Research, Nepal Development Society, Pokhara; [3]Department of International Health, Johns Hopkins Bloomberg School of Public Health, E5530, 615N Wolfe St, E8012, Baltimore, MD 21205; [4]Hemodialysis, National Kidney Center Nepal, Kathmandu; [5]Research, Nepal Development Soceity, Pokhara; [6]Department of Occupational and Environmental Medicine, (OEM), Gothenburg University, Traryd, [7]CEO/Research, La Isla network.org, Alpharetta GA 30005, [8]Department of Epidemiology, Bloomberg School of Public Health, Baltimore, Maryland, 21205

Introduction: Many young Nepali migrant workers developed end-stage renal disease (ESRD) while working abroad. Mandatory predeparture tests done estimate a very low prevalence of kidney disease. The etiology of kidney disease remains unknown, but exposure to recurrent heat stress and chemicals have been suggested as potential risk factors. Our study aims to understand the demographic and occupational characteristics of returning migrant workers (RMW) currently on hemodialysis.

Methods: Cross-sectional study was conducted in 2 large hemodialysis centers in Kathmandu from April through May of 2023. Questionnaire with emphasis on occupational exposure to heat and chemicals and migrant history were administered to all patients 18-80 years of age receiving in-center hemodialysis. Ethical approval was obtained from the Nepal Health Research Council.

Results: A total of 339 patients were included in the study (mean age 46.2 ±13.7 yrs.) Among them 28% were returnee migrant workers, of whom 87% were male and 68% worked in the Gulf Cooperation Council (GCC) and Malaysia. Returnee migrant workers were on average 6.4 years younger than non-returnee migrant workers (P <0.001). More than a half of returnee migrant workers were younger than 40 years, compared to 30% of non-returnee migrant workers (P <0.001). The median duration of work abroad was 12 years (IQR 9-16). Health problems were the reason for the return of more than half of the

conclusion

- Clinicians should maintain a state of increased alertness with regards to the potential occurrence of WRN who exhibit hematuria and elevated creatinine levels while on warfarin therapy, even if their INR remains within the normal range.

- Considering most patents of WRN have an underlying glomerular disease (mostly IgA nephropathy), the use of steroids and immunosuppressive drugs may appear to e an attractive option, particularly in patients who are unable to replace warfarin with direct oral anticoagulants (NOACs).

see original article on page 181

Warfarin-related nephropathy: another newly recognized complication of an old drug

Dana V. Rizk[1] and David G. Warnock[1]

Since its approval in the 1950s, warfarin has been the most often prescribed anticoagulant, with attendant risks of bleeding. Brodsky *et al.* describe another potential complication of warfarin therapy. Warfarin-related nephropathy (WRN) has been described in patients with chronic kidney disease and appears to accelerate the rate of progression and increase the risk of death. The interactions between warfarin and chronic kidney disease are complex, and the recognition of the potential complications is expanding.

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Patients with chronic kidney disease (CKD) are at increased risk of thromboembolic events; however, anticoagulation in this patient population has always need significantly lower warfarin doses to achieve therapeutic anticoagulation, spent less time in target international normalized ratio (INR) range, and frequently

WRN. A major limitation of this retrospective review of administrative records was the reliance on medical coding for the diagnosis of CKD (ICD-9 codes 585.1 through 585.5 or 585.9, excluding 585.6). Unfortunately, there was no systematic examination of urine protein excretion, which could well be an independent risk factor for overcoagulation associated with loss of procoagulant factors in the urine and might have allowed better characterization of the actual incidence and severity of CKD in patients receiving warfarin therapy.

The lack of reported hematuria in the setting of WRN despite the presence of renal tubular obstruction by red blood cells[4] on kidney biopsy is challenging, especially if the diagnosis has to be exclusively based on pathology in subjects at risk who are already overcoagulated.[4] The proposed diagnostic criteria for WRN include a 0.3 mg/dl increase in serum creatinine in patients who have had a measured INR greater than 3 within the

INTRODUCTION

- **Since its approval in the 1950s, warfarin has been the most often prescribed anticoagulant, with attendant risks of bleeding.**
- **Brodsky *et al.* describe another potential complication of warfarin therapy.**

- Warfarin has a narrow therapeutic range and interacts with a variety of commonly used medications and dietary factors, especially leafy green vegetables.
- Its use requires close monitoring, and hemorrhage remains its most common and feared complication.
- **In CKD patients, that risk is increased more than twofold.**
- In a recent study, patients with severe CKD were found to need significantly lower warfarin doses to achieve therapeutic anticoagulation, spent less time in target international normalized ratio (INR) range, and frequently were over-anticoagulated.
-

RISK FACTORS OF WRN

- CKD
- age,
- diabetes mellitus,
- hypertension, and
- cardiovascular disease being significant risk factors.

- The proposed diagnostic criteria for WRN include a 0.3 mg/dl increase in serum creatinine in patients who have had a measured INR greater than 3 within the previous week.

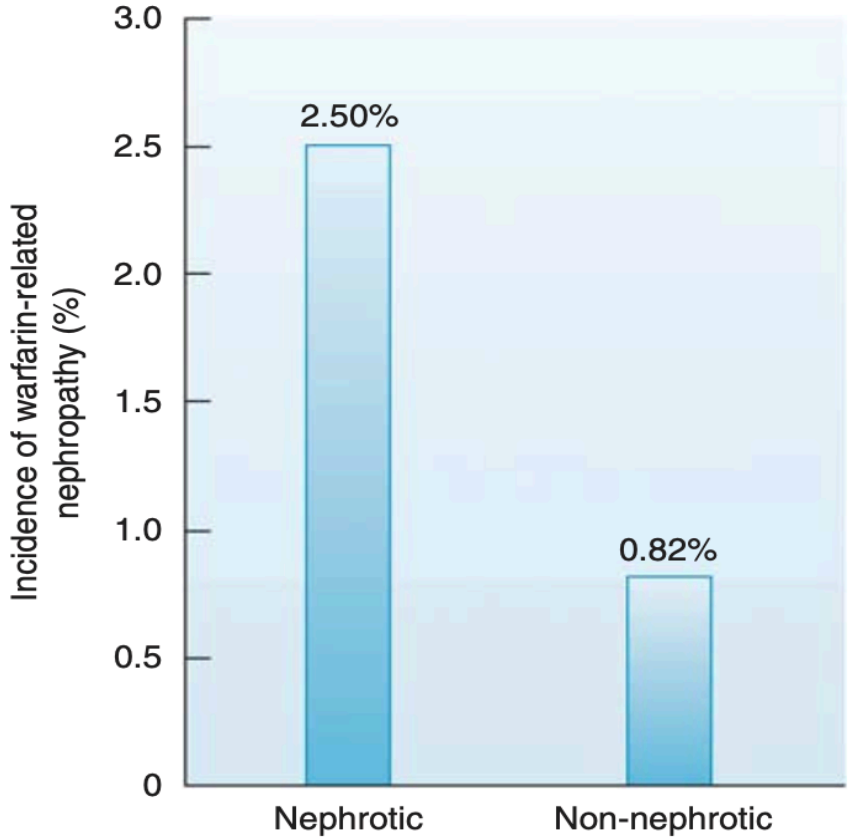

Figure 1 | Apparent incidence rates of warfarin-related nephropathy in CKD patients with nephrotic syndrome and CKD patients without nephrotic syndrome. (Adapted from Table 1 of Brodsky *et al.*[3])

Case Report

Warfarin-related Nephropathy

Abstract

Warfarin-related nephropathy also referred to as anticoagulant-related nephropathy (ACRN) is a type of acute kidney injury (AKI) that may be caused by excessive anticoagulation with warfarin and other anticoagulants. Despite the well-described histological entity, the clinical course and approach to ACRN in patients requiring life-long anticoagulation are however not well described in the literature. We report a 50-year-old Indian woman who was on prolonged anticoagulant therapy post-mitral valve replacement. She presented with AKI, and renal biopsy was suggestive of ACRN. Steroids were given and her creatinine levels reached within the normal range in 2 weeks. A presumptive diagnosis of ACRN should be made if a severe warfarin coagulopathy is present and if other causes of AKI have been excluded, in patients with chronic anticoagulant therapy. Renal function should be monitored regularly in patients who are on anticoagulant therapy.

Keywords: *Acute kidney injury, anticoagulant-related nephropathy, corticosteroids, mitral valve replacement, warfarin*

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Anticoagulant-related nephropathy (ACRN)

- Warfarin-related nephropathy also referred to as anticoagulant-related nephropathy (ACRN) is a type of acute kidney injury (AKI) that may be caused by excessive anticoagulation with warfarin and other anticoagulants.
- Despite the well-described histological entity, the clinical course and approach to **ACRN in patients requiring life-long anticoagulation** are however not well described in the literature.
- We report a 50-year-old Indian woman who was on prolonged anticoagulant therapy post-mitral valve replacement.
- She presented with AKI, and renal biopsy was suggestive of ACRN.
- **Steroids** were given and her creatinine levels reached within the normal range in 2 weeks.
- A presumptive diagnosis of ACRN should be made if a severe warfarin coagulopathy is present and if other causes of AKI have been excluded, in patients with chronic anticoagulant therapy.
- Renal function should be monitored regularly in patients who are on anticoagulant therapy.

ACRN

- **A definitive diagnosis is made by renal biopsy.**
- Incidence of AKI in the largest cohort of warfarin using patients was 20.5% overall and 33% in patients with a history of chronic kidney disease (CKD).
- Other independent predictors of AKI risk in these patients were:
- **age,**
- **diabetes mellitus,**
- **heart failure,**
- **hypertension, and**
- **glomerulonephritis particularly with nephrotic syndrome**

pathogenesis of ACRN

- Kidney biopsy in a subset of these patients showed obstruction of the renal tubule by RBC casts, and this appears to be the dominant mechanism of AKI.
- The initiating event in the pathogenesis of ACRN appears to be glomerular hemorrhage, caused by

excessive anticoagulation due to warfarin or other anticoagulants.

- Glomerular hemorrhage results in the formation of obstructing RBC casts within the renal tubules.
- The glomeruli show little or no abnormalities by immunofluorescence, light, or electron microscopy.

management of warfarin-related nephropathy (WRN)

- The management of warfarin-related nephropathy (WRN) in patients requiring prolonged anticoagulation poses a management dilemma.

- The role of steroids is not clear in WRN.
- **The anti-inflammatory effect of steroids may be useful in mitigating the onset of interstitial fibrosis as a consequence of WRN**.
- Temporary interruption of anticoagulation may ameliorate glomerular bleeding and result in stabilization of the renal function.

The initiating event in the pathogenesis of ACRN appears to be glomerular hemorrhage, caused by

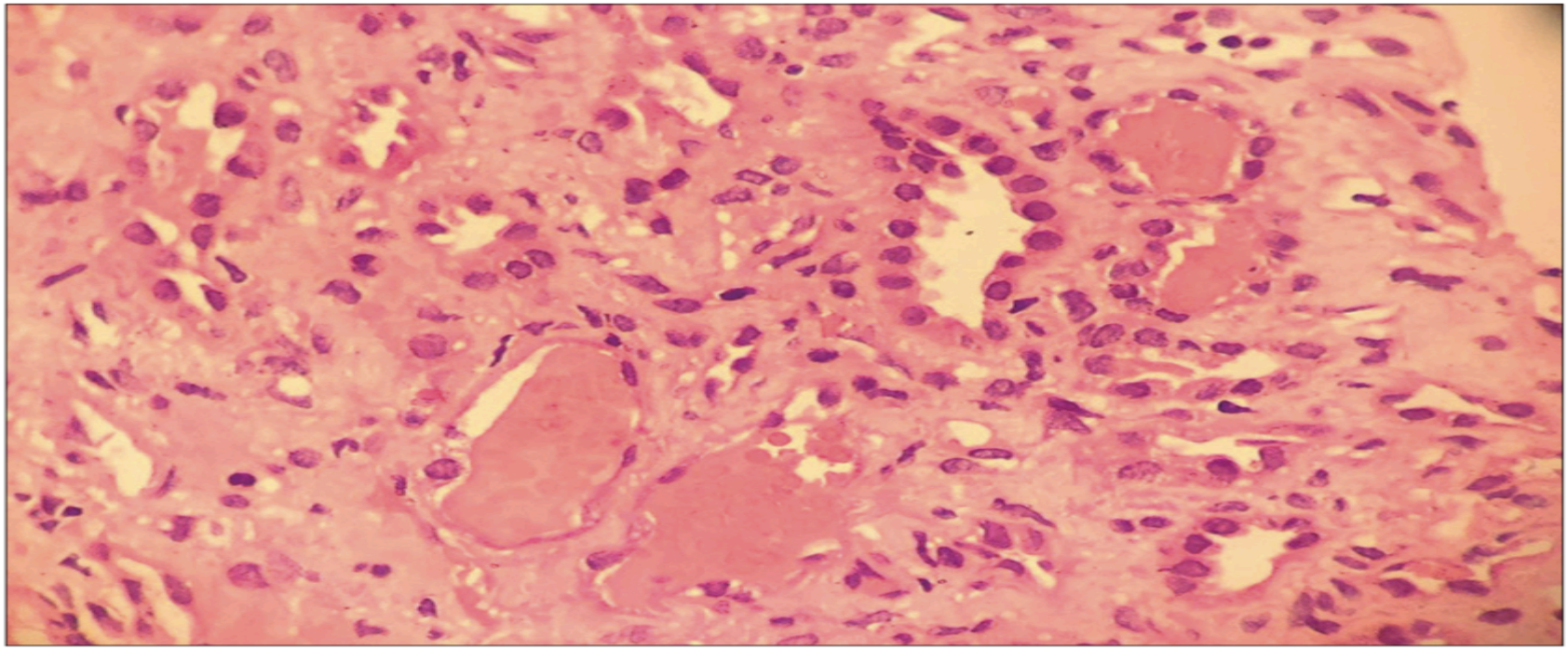

Figure 1: Renal biopsy findings: tubules show intraluminal red cell casts. Interstitium shows infiltrate of lymphocytes and neutrophils

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Warfarin-Related Nephropathy Manifested as Diffuse Mesangial Proliferative Glomerulonephritis

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Warfarin-Related Nephropathy Manifested as Diffuse Mesangial Proliferative Glomerulonephritis

- Warfarin is associated with anticoagulant-related nephropathy (ARN), one of the potential side effects.
- This is evidenced by a progressively increasing number of detected cases of deterioration in the kidney function even in patients with normal baseline function (GFR {glomerular filtration rate}) in addition to the chronic kidney disease (CKD) patients who are already vulnerable to ARN.
- There has been a clinical correlation in a rapid decline of kidney function and international normalized ratio (INR) levels of greater than **3**.
- We want to emphasize the importance of monitoring kidney function regularly and adjusting the appropriate doses of warfarin.
- We present a case of a 57-year-old female who was on warfarin for the mechanical aortic valve, presented with acute kidney injury and supratherapeutic INR.
- Her renal biopsy showed **diffuse mesangial proliferative glomerulonephritis**.

MPGN

- Independent of the chronic kidney disease status, **glomerular hemorrhage** and renal tubular obstruction by red blood cells can be seen in patients who were treated with excessive warfarin.
- The underlying molecular mechanism for WRN was thought to be **warfarin-induced thrombin depletion**; a similar mechanism of action may also be seen with other anticoagulants such as dabigatran .
- **However, newer studies have hinted at an alternative mechanism involving reductions in activated protein C and endothelial protein C receptor signaling** .
- Mesangial proliferative glomerulonephritis **(MPGN)** is characterized by a diffuse or focal increase in the number of mesangial cells and expansion of the extracellular matrix in glomerular mesangium with or without immunoglobulin or complement deposition .
- We report an interesting case of a 57-year-old female on warfarin for mechanical aortic valve who presented with AKI requiring hemodialysis and was found to have diffuse mesangial proliferative glomerulonephritis and warfarin-related nephropathy on renal biopsy.

Discussion

- Warfarin-related nephropathy (WRN) is a common complication of warfarin therapy.
- However, it is underdiagnosed, as nephrologists are hesitant to perform a kidney biopsy on patients taking anticoagulants .
- In a study involving 15,258 patients taking warfarin with an INR >3, 20.5% developed AKI within one week .
- Risk factors that predispose one to have WRN are **CKD, old age, diabetes mellitus, diabetic nephropathy, hypertension, and cardiovascular disease, specifically heart failure, and GN** .
- In the same study, 33.0% of those who have CKD had WRN as opposed to 16.5% of those who do not have CKD.
- Patients may present with hypertension, volume overload, poor urine output, hematuria (gross or microscopic), proteinuria, and elevated creatinine.
- Prompt recognition of ARN is critical, as it is associated with accelerated progression of chronic kidney disease, and significant increases in short-term and long- term all-cause mortality.

worked up of WRN

- They should be worked up with **urinalysis, urine electrolytes analysis, and kidney ultrasound .**
- Although hematuria is a common finding in WRN, its absence does not rule it out.
- Therefore, any patient who presents with an AKI with a history of supratherapeutic INR and no known etiology should be considered as WRN.
- **Treatment for WRN/ARN is supportive.**
- The anticoagulant should be adjusted within the therapeutic range .

prevention of WRN and monitoring those who use warfarin

- Wheeler et al. made the following recommendations:
- (1) check INR and kidney function every three to four weeks during the first three months of anticoagulation,
- (2) monitor the renal function every three to six months with those who have a creatinine clearance of <60 mL/min,
- (3) assess the renal function of any patient with supratherapeutic INR as soon as possible,
- (4) do renal workup on any patient on anticoagulants with acute worsening of renal function.


Oxidative stress damage to tubules by RBCs
Glomerular hemorrhage and renal tubular obstruction by red blood cells
Apoptosis of glomerular endothelial cells
Warfarin-related Nephropathy
Atheroembolism
Interstitial nephritis
Direct effects of warfarin on the glomerulus

Conclusions

- Warfarin-related nephropathy or anticoagulant-related nephropathy should be considered if severe warfarin coagulopathy is present and if other causes of acute kidney injury have been excluded in patients on chronic anticoagulant therapy.
- Coagulopathy, especially if INR is greater than 3, CKD is the strongest risk factor for the development of warfarin-related nephropathy.
- Renal function should be regularly monitored in patients on anticoagulant therapy.
- Any patient receiving anticoagulation with acute worsening of renal function needs an immediate renal workup, including urine analysis, urine electrolyte analysis, and renal ultrasound.
- If that workup is negative or demonstrates isolated hematuria, ARN should be strongly considered in the differential diagnosis.
- ARN can be prevented by adjusting warfarin dosage especially in patients with CKD.
- Recovery of renal function in patients with anticoagulant-related nephropathy varies, with some patients reverting back to baseline once INR is stabilized while some patients may not have any recovery.
- **The role of steroids in warfarin-related nephropathy is unclear which should be investigated in further studies.**