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RENAL ATHEROEMBOLIC DISEASE IN THE AGING POPULATION: A CRITICAL ANALYSIS OF PATHOLOGY, DIAGNOSIS, AND THERAPEUTIC APPROACHES

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ABSTRACT

Background: The prevalence of renal atheroembolic disease has surged alongside the ageing population, intensified anticoagulation therapy, and increased vascular interventionism. This review aims to present a contemporary overview of this pathology, covering risk factors, diagnostics, histopathology, and therapeutic strategies.

Methods: A comprehensive literature search was conducted to gather pertinent studies and clinical reports related to renal atheroembolic disease. Key databases were queried, and relevant articles were selected based on their relevance to the topic.

Results: Renal atheroembolic disease typically manifests in patients with diffuse atherosclerosis, often following triggers such as aortic surgery, invasive procedures (e.g., angiography, coronary angioplasty), or anticoagulant/fibrinolytic therapy. Clinical presentation varies widely due to the occlusion of small arterial vessels by cholesterol emboli originating from atheromatous plaques, primarily in the abdominal aorta or its major branches. The kidneys, owing to their proximity and high blood flow, are frequently affected. Despite its clinical significance, the systemic nature of atheroembolism complicates diagnosis, leading to frequent underrecognition.

Conclusion: This manuscript offers an updated synthesis of renal atheroembolic disease, emphasizing its contemporary clinical relevance. Understanding the risk factors, diagnostic challenges, histopathological features, and therapeutic options is crucial for effective management and improved outcomes in nephropathic patients.

KEYWORD: atherosclerosis, cholesterol emboli, contrast medium, acute kidney injury, chronic kidney disease.

Introduction

Author(s)	Year	Title
Arroyo-Andrés, Agud-Dios et al.	2024	Atheroembolic Renal Disease: The "Cinderella" of Nephrology?
Balmforth, Whittington et al.	2024	Enhancing Awareness and Management of Atheroembolic Complications: A Call to Action

Materials and methods

A bibliographic search was conducted on Pubmed, Scopus and Web of Science, searching for the keywords “atheroembolic” AND “renal” AND “disease” within the title or abstract, without time restriction. Two reviewers (S.C., W.M.) were responsible for selecting the titles relevant to the topic using the following inclusion criteria (GOUDA, DAS et al. 2024):

a. language other than English and Italian;
b. repeated works by the same authors;
c. Lack of relevance of the data reported with the central theme of the review.

The reviewers therefore selected the studies for inclusion in the review by consensus. In case of doubt about relevance, the results of the bibliographic search were assessed as eligible for inclusion in the paper only after reading the entire text.

Results

The research, conducted through the search above engines, allowed us to initially identify 116 titles, which were reduced to 115 after removing a duplicate present in the list. Furthermore, 39 additional titles were identified starting from the bibliographical references of the same articles already mentioned. After reading and eliminating irrelevant articles, 76 articles were brought up for discussion (Figure 1) (Jayanatha, Kumar et al. 2024).

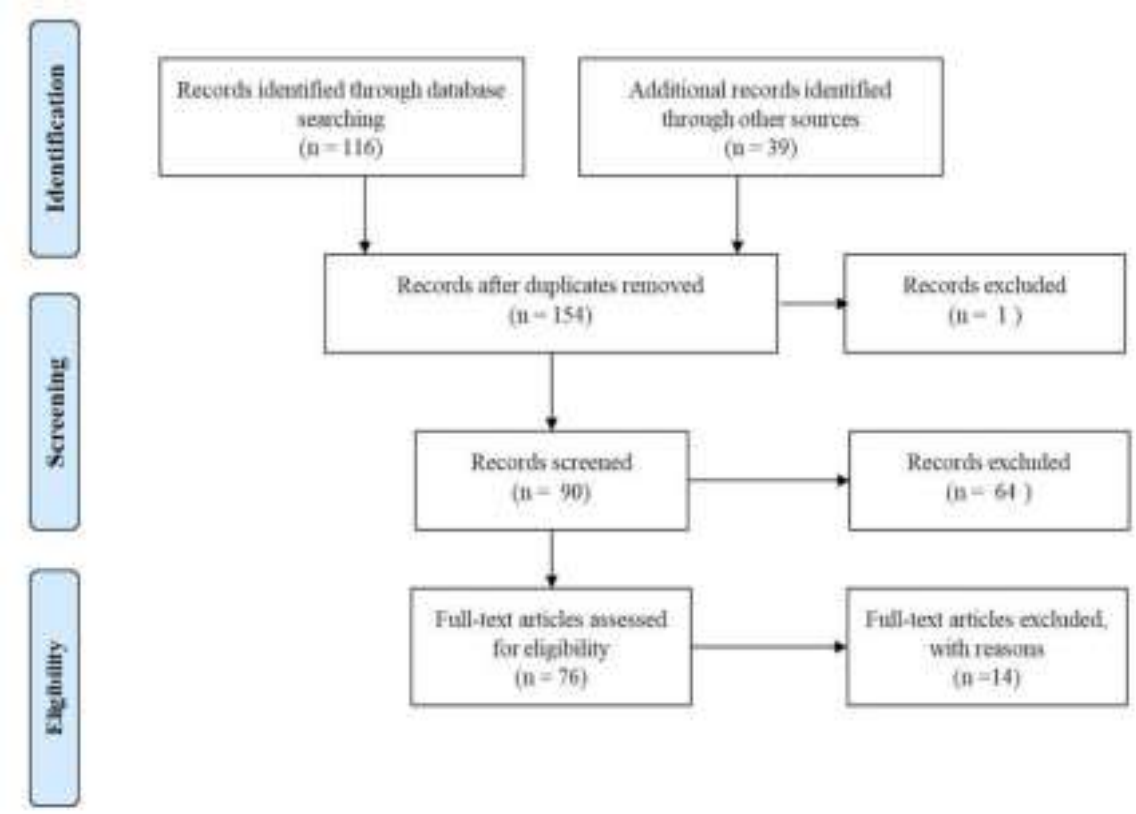

Figure 1: Results presented according to PRISMA diagram

Aetiology and risk factors

Atheroembolism complicates atherosclerosis and shares risk factors with it, such as age, male sex, diabetes, arterial hypertension, hypercholesterolemia and cigarette smoking. The first to describe AERD as a pathological condition was the German pathologist Panum in 1862. However, only in 1967 did it pass from a "simple anatomical-pathological curiosity" to a well-defined clinical entity when Moldveen-Geronimus and Meriam advanced the suspicion that an embolization of cholesterol crystals mediated the picture of "purple toes" observed during dicoumarol therapy. In a 1987 review, Fine et al., analyzing 221 cases published in the English literature, noted an incidence of other embolic diseases in autopsies of an unselected population of 0.15-3.4% (Jin, Chen et al. 2024). Although the presentation of AERD can be spontaneous in 30% of its manifestations, due to intravascular phenomena linked to shear stress, predisposing factors (Table I) and triggering factors are well identifiable. Among the former, we include age over 60, male sex, diabetes, arterial hypertension, hypercholesterolemia and cigarette smoking (all factors that predispose to the onset of atherosclerosis); the triggering factors, iatrogenic in more than 70% of cases, can be angiography and coronary angiography, cardiovascular surgery, aortic mechanical trauma (induced by radiological catheters or by vessel manipulation), thrombolytic or anticoagulant therapy. These factors can determine the shattering of the atherosclerotic plaque and the production of cholesterine crystal emboli, with possible systemic dissemination. Much more rarely, AERD can complicate an inflammatory disease of the large vessels (Takayasu arteritis, systemic vasculitis, thromboangiitis obliterans) (Kawai, Finn et al. 2024).

Predisposing factors AERD	AERD precipitating factors
Hypertension	Arterial catheterization
Male sex	Angiography
Age >65 years	Cardiovascular surgery
Smoking	Thrombolytic therapy or anticoagulants

Table I: Predisposing and triggering factors for AERD

Incidence

The true incidence of AERD is not precisely known and is often underestimated as a cause of renal failure. As early as 1993, Lye et al. reported 129 cases of other embolic disease with clinical evidence of renal involvement. The ability with which the incidence of the disease is reported in the literature often depends on confounding phenomena such as, for example, the differences with which the design of the published studies was designed or on sampling bias. In some studies, the predictive value of traditional risk factors has been emphasized by creating a clinical score based on age, positive clinical history for symptomatic vascular disease, dyslipidemia and abdominal bruit, while in clinical studies based on a follow-up short-lived after the invasive vascular procedure, the true incidence of AERD tends to be underestimated (Li, Varcoe et al. 2024).

Mayo and collaborators, in a 1996 review, estimated that between 5-10% of all cases of acute renal failure admitted to the hospital could be due to AERD. The results of retrospective studies deriving from autopsies or biopsy studies, such as those performed by Preston et al. of 334 patients aged 65 years or older who underwent renal biopsy for acute renal failure (n = 55), subacute renal failure (n = 72), chronic renal failure (n = 57), proteinuria (n = 137) and hematuria (n = 13), may, however, overestimate the real incidence of the disease as they also include subclinical cases (Muhammad, Zhang et al. 2024).

Clinic

AERD must be considered as the renal expression of a broader systemic picture, as atheroembolism ubiquitously affects the various vascular districts, with random distribution affecting the downstream organs, allowing the generation of great phenotypic variability in the clinical picture. It wins very evocative definitions such as "puzzling event" and "great masquerader" precisely because of its ability to mimic other pathological entities. The main clinical characteristics described by the authors in the literature have been summarized in Table II (Murphy 2024).

	Belenfant [75]	**Falcon [41]**	**Fine [9]**	**Lye [25]**	**Schoolchildren [5]**	**Thandhani [6]**
Eosinophilia (%)	59	80	73	71	67	22
Retinal emboli (%)	22	7	6	10	7	25
Skin lesions (%)	90	75	35	43	75	50
Central nervous system (%)	4	10	0	12	10	23
Gastrointestinal manifestations (%)	33	12	10	10	12	29

Table II: Clinical manifestations in AERD

AERD can present with a general malaise and vague and nonspecific symptoms such as asthenia, fever, myalgia, epistaxis, headache and weight loss up to - in the most severe forms - cachexia, mimicking present conditions in other systemic pathologies for which it is being diagnosed differential (pauci-immune vasculitis, infectious conditions). Pulmonary involvement, characterized by alveolar haemorrhage mimicking systemic vasculitis, has been described in some patients. The pathogenetic mechanisms of pulmonary haemorrhage remain poorly understood: the local inflammatory reaction caused by emboli could play a role (Murphy 2024).

The most frequent clinical manifestation is related to chemoembolization of the skin with the appearance of "blue toe syndrome" or *livedo reticularis*. Furthermore, mesenteric anginas are very frequent (which can also cause very severe conditions with intestinal ischemia, gastrointestinal bleeding or pancreatitis), with manifestations affecting the central nervous system with frequent transient ischemic attacks or drops in *all*. In general, ocular or cerebral manifestations result from the shattering of an atheroembolic plaque located at the level of the ascending aorta or aortic arch. Emboli arising from the aortic root or proximal segments of the coronary arteries can cause sudden cardiac death. In autopsy studies, subclinical involvement of the adrenal glands, testes, prostate, thyroid, and virtually every other organ has been reported (Sharma, Simon et al. 2024).

The visceral manifestations of AERD are often caused by emboli originating from an atheroembolic plaque located at the level of the descending thoracic aorta and abdominal aorta. Due to its proximity to the abdominal aorta and the high blood flow that normally reaches it, the kidney becomes a privileged target during systemic atheroembolism. Renal damage from atheroembolism is, in fact, far from rare, as demonstrated by the works of Haas et al. Renal failure due to AERD can manifest itself in a heterogeneous manner, such as (Arroyo-Andrés, Agud-Dios et al. 2024):

a) **Acute kidney injury** (AKI), therefore, as acute onset renal failure, usually within a week of an endovascular procedure, is a direct consequence of the massive migration of cholesterol crystals in the renal intraparenchymal arteries with a rapidly progressive evolutionary picture.
b) **Subacute renal damage**, in which renal failure is progressive and occurs “delayed” after periods of stable renal function. In this context, renal failure is usually observed between 3 and 5 weeks

after a documented event. This manifestation of AERD is probably due to a combination of the plaque embolization effect and the endothelial inflammatory reaction effect from a foreign body.

c) **chronic renal failure**(IRC). The latter occurs less frequently and can be attributed to damage from nephroangiosclerosis or ischemic nephropathy. The clinical consequences of intimal proliferation and narrowing of the vascular lumen are common features.

Only rarely does organ damage exclusively concern the renal district, often being associated with signs of gastrointestinal and skin embolization. In a minority of cases, the other embolic disease proceeds in a clinically silent manner, i.e., in the absence of extrarenal signs and symptoms. Biopsy (renal or skin) is performed only rarely, and the diagnosis of AERD is therefore not made (Balmforth, Whittington et al. 2024).

The clinical course of renal failure can be heterogeneous and lead to replacement treatment in 28-61% of patients with acute or subacute disease. A percentage of patients between 20-30% present a partial recovery of renal function after a variable period of dialysis support; this recovery may be due to the resolution of endothelial inflammation *restoration to complete* acute tubular necrosis in ischemic areas. The renal manifestations of other embolic diseases are generally different from those seen in patients with thromboembolism. Thromboemboli occurs primarily in patients with cardiac arrhythmias (atrial fibrillation or flutter) or a previous myocardial infarction. They tend to produce complete arterial occlusion and, consequently, renal infarction, leading to flank pain, hematuria and increased lactate dehydrogenase (GOUDA, DAS et al. 2024).

Particular forms of AERD

The transplanted kidney is not free from the complications of AERD, although this represents a rare finding, with a frequency of 0.39%-0.47%. The incidence of this phenomenon in the transplanted kidney is probably underestimated due to a bias linked to biopsy needles that are too small or sampling errors. The consequences of atheroembolism on the transplanted kidney were described for the first time in 1985 by Cosio et al. following the finding of cholesterol emboli on the transplanted kidney sample explanted in a patient who had developed oliguria immediately after cadaveric renal transplantation (Jayanatha, Kumar et al. 2024).

Two modes of presentation of AERD in the transplanted kidney can be identified: an early form and a late form. In the early form of graft AERD, emboli are released from the donor's arteries during organ harvesting (Figure 2) or, less frequently, from the recipient's arteries during the preparation of the anastomosis. The late form of AERD, however, can occur even years after surgery. It is generally observed in grafts with stable function and is associated with the same risk factors and precipitating events identified in the general population. According to the literature, the prognosis of early forms is worse than late forms, in which the function of the graft seems to recover in most cases (Jin, Chen et al. 2024).

The reason for this difference could be attributable to extensive embolization in an atherosclerotic donor during organ procurement. Furthermore, among the early forms, AERD of the transplanted kidney starting from the donor's arteries has a worse prognosis than AERD of the graft that develops starting from the donor's arterial vessels. Since there is an increase in the trend to accept donors and recipients over the age of 60 and to use marginal donors with advanced atherosclerosis, the incidence of other embolic renal disease in kidney transplantation will likely increase in the coming years. It is possible to reduce the risk of AERD in the transplanted kidney with very careful evaluation of organ donors and minimal manipulation of the aorta, thus mobilizing the kidneys without blocking the aorta (Kawai, Finn et al. 2024).

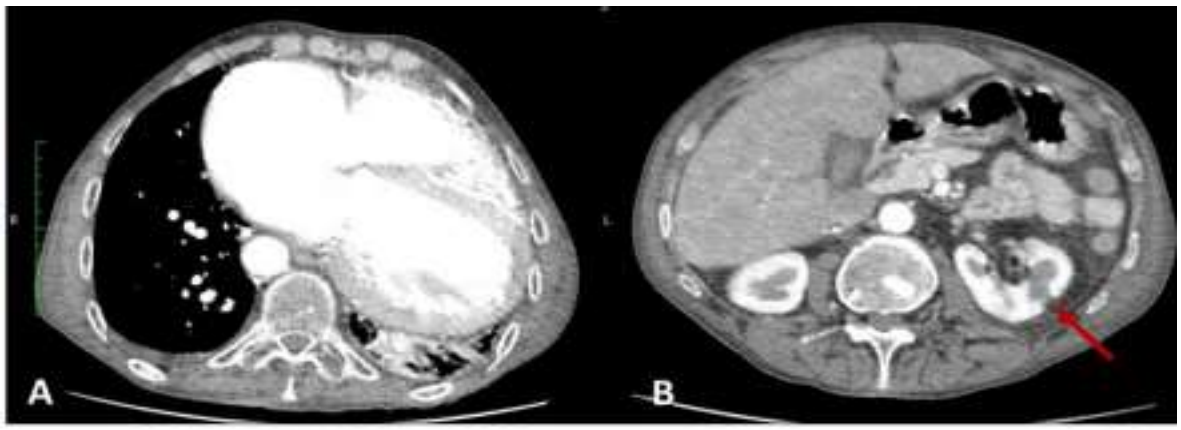

Figure 2: 50-year-old patient who has congenital heart disease (Tetralogy of Fallot) with cardiomegaly and chronic ischemic heart disease (Figure 2A) is being treated with dicoumarols. The red arrow in Figure 2B indicates an area of renal cortical defect likely related to a renal infarction (courtesy of Doctor C. Trombatore, Specialist in Radiology, G. Di Maria Hospital, Avola (SR))

Diagnosis

Developing a diagnosis of AERD can be complicated if there is a causal link between the *thought-provok*ing pathogen and loss of renal function. The nuanced presentation and the wide spectrum of phenotypic manifestations, the polymorphism of the clinical picture due to the systemic character of the disease and the ubiquitous diffusion of other embolic plaques in the organism make the "great masquerader" [22] extremely labile and elusive in the diagnostic process routine (Li, Varcoe et al. 2024).

The typical patient in whom to look for AERD is over 60 years of age, with a history of hypercholesterolemia, arterial hypertension, smoking and acute renal failure in the context of an endovascular procedure or anticoagulant therapy. Often, laboratory data such as anaemia, thrombocytopenia, alteration of inflammation indices, erythrocyte sedimentation rate (ESR) and transient hypocomplementemia are not sufficiently conclusive. The alteration of nitrogen retention indices may remain only anomalous data. Hypercholesterolemia is a well-known risk factor for atherosclerosis, of which embolization can be considered a direct complication. Numerous authors identify hypercholesterolemia as an important diagnostic element for defining the disease (Muhammad, Zhang et al. 2024).

Urinalysis can be useful: the appearance of modest proteinuria, microhematuria, hyaline and granulocytic casts, although not specific, can be an expression of ischemic damage and an increase in the permeability of the glomerular membrane. The sediment, unlike vasculitis, does not have a nephritic character. Hematuria is found in 33-40% of patients. Subnephrotic proteinuria is found in approximately 55-60% of patients. In some cases, proteinuria in the nephrotic range has been described in the absence of evident nephrotic syndrome, with lesions proven on biopsy of membranous glomerulonephritis, glomerulosclerosis focal or diabetic glomerulopathy. Leukocytosis with eosinophilia [66], which occurs during the acute phase, probably represents the most characteristic biochemical alteration and is linked to immune activation on the exposed surface of microemboli, while eosinophiluria is less suggestive (Murphy 2024).

With rare exceptions, the search for ANCA is generally negative, making the differential diagnosis of vasculitis easier. Other laboratory anomalies that can be found in the context of AERD concern hyperamylasemia (which confuses the diagnosis, directing it towards pancreatitis), increased creatine phosphokinase (CPK) (which suggests myositis), hypertransaminasemia and the increase in alkaline phosphatase and lactate dehydrogenase, a possible outcome of hepatic embolization or, although rare, of a severe renal infarction (Sharma, Simon et al. 2024).

The correct diagnosis can only be made with a renal biopsy, demonstrating the presence of cholesterol crystals inside the renal vessels and glomeruli (see the histology paragraph). However, a

biopsy cannot always be performed due to the advanced age of the patients, nephroangiosclerosis and the small size of the kidneys. Until a few years ago, in diagnostic imaging, the diagnosis of AERD was performed by selective angiography or CT angiography. With the latter method, after infusion of the contrast medium, the ischemic areas appear as non-perfused areas which usually have a wedge shape (with the base facing the renal capsule and the apex facing the hilum) (Arroyo-Andrés, Agud-Dios et al. 2024).

Similarly, it is possible to highlight an enhancement of the cortex as an expression of collateral flows. However, due to the nonspecific presentation, the sudden onset of the atheroembolic event and renal failure, CT angiography is not a frequently requested diagnostic investigation in the context of AERD, so the diagnosis is often delayed (and even lost). The finding of a clinical case already evolving or resulting in ischemic problems is not uncommon (Figure 3) (Balmforth, Whittington et al. 2024).

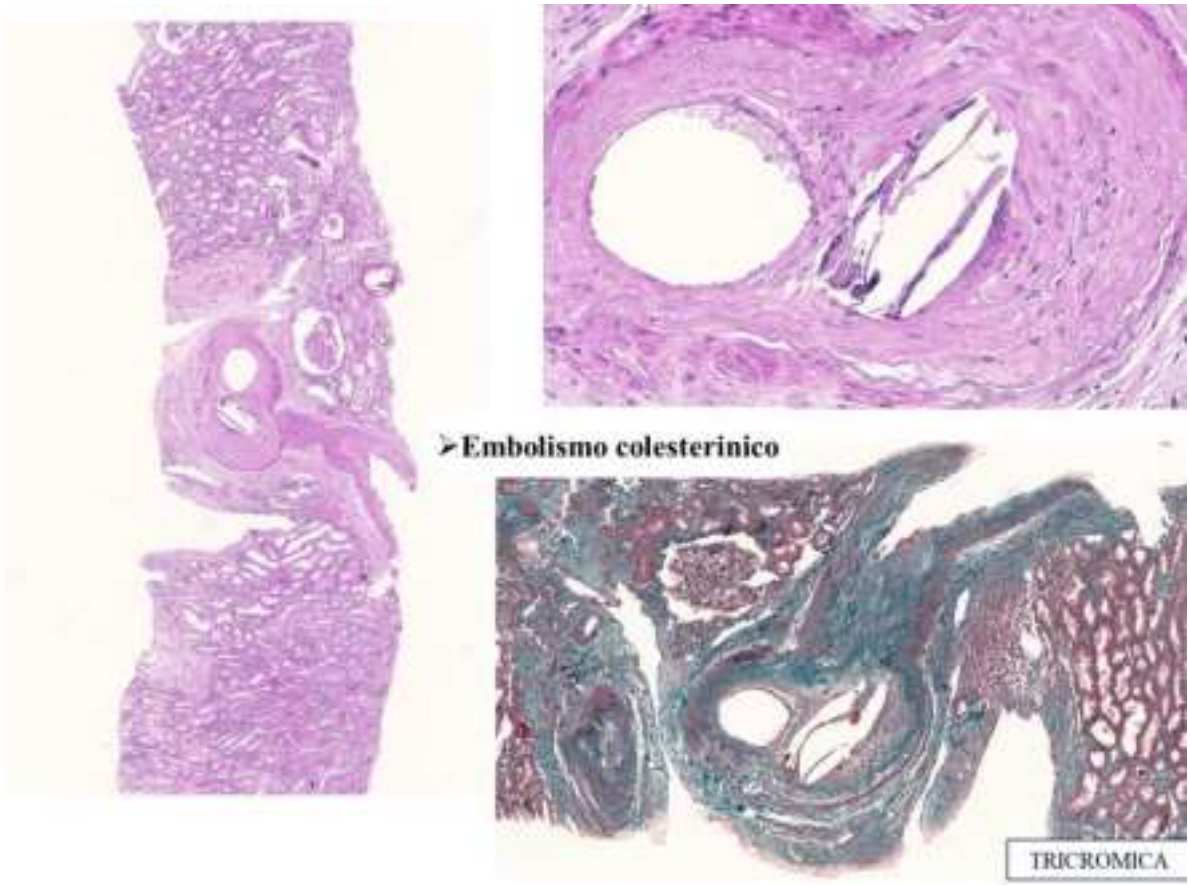

Figure 3: Cholesterol embolus in kidney donor, male, 77 years old, hypertensive, cause of death: spontaneous cerebral haemorrhage (courtesy of Dr A. Barreca)

The use of View-shared Compressed Sensing-based Dynamic Contrast-Enhanced Magnetic Resonance Imaging (VCS DCE-MRI) in the study of residual renal function appears still experimental. A preliminary study conducted in rabbits verified the feasibility of VCS DCE-MRI for assessing renal function, and the strategy could provide a valuable tool for identifying AERD. Lately, however, ultrasonographic methods have become increasingly useful. During damage to the microcirculation due to atheroembolic involvement of the afferent and interlobular arterioles, B-Mode ultrasound does not allow us to detect pathognomonic signs of the disease. At the onset of AERD, the kidney generally maintains a preserved or modestly reduced diameter with an irregular profile (GOUDA, DAS et al. 2024).

Moving away from the acute event, the parenchyma can reduce in thickness and appear hyperechoic, degenerating into acquired cysts and sclerolipomatosis of the renal sinus and then

resulting in ultrasound pictures of no univocal interpretation, which end up being confused with the images of nephroangiosclerosis linked to patient comorbidities (hypertension, diabetes, ageing). The morphological study of the aorta and large vessels appears useful in ultrasound diagnostics, as it can highlight the marked mixed atheromasia represented by vegetating or flat plaques (Figure 4) (Jayanatha, Kumar et al. 2024).

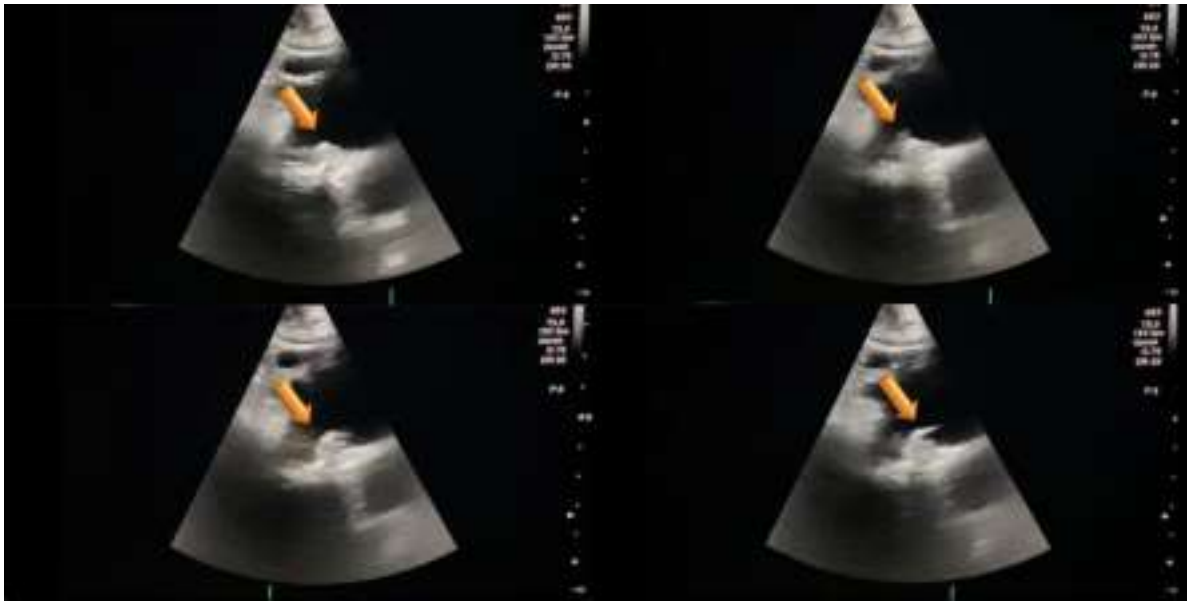

Figure 4: Atheroembolic plaque at the level of the ascending aorta, at the junction with the supra-aortic trunks (courtesy of Dr Giovanni Tasca, UOC of Cardiology, Modica)

Evaluation in Color and Power Doppler allows you to obtain more information. Colour Doppler highlights a "minus of colour" as an expression of the reduced perfusion of the ischemic areas. Power Doppler, thanks to its greater sensitivity, allows us to discriminate with greater accuracy the normally perfused areas from the ischemic ones: in a normal kidney, homogeneous blushing is observed. In contrast, in an ischemic kidney, we notice areas without colour. Furthermore, the spectral analysis allows us to detect an increase in the resistance index (high systolic and lowly significant diastolic waves) in the arterial vessels upstream of the embolus (Jin, Chen et al. 2024).

The investigation is even more accurate if implemented with the use of a contrast medium. In this way, it is possible to overcome, at least partially, the problems associated with the patient's constitution, the patient's inability to maintain apnea or inadequate preparation for the exam. Certainly, the ultrasonographic finding is nonspecific. However, the non-invasiveness (remember that the use of iodinated contrast agents is particularly harmful in subjects with renal insufficiency) and the relatively low cost make the Color Power Doppler ultrasound a fundamental step in the modern diagnostic process (Kawai, Finn et al. 2024).

Contrast-enhanced ultrasound (CEUS), overcoming the intrinsic limitations of Doppler, such as low diagnostic accuracy and the insonation angle unfavourable to the renal poles, allows the evaluation of renal perfusion in almost all situations. In the context of infarction, CEUS can show infarcted regions as areas without contrast enhancement, often with wedge-shaped morphology. The diagnostic sensitivity of CEUS in the studies by Bertolotto et al., although the use of CEUS in the specific context of AERD was not explored in detail, was similar to angiography and CT. The excellent spatial resolution of CEUS allows us to differentiate between renal infarctions and cortical ischemia. It is possible to recognize the enhancement of the segmental, interlobar and arciform vessels versus the absence of enhancement of the interlobular vessels of the affected renal cortex. Among the second-level diagnostic potentials, ultrasound endoscopy appears to be of possible use. However, further studies are needed (Li, Varcoe et al. 2024).

Histology

In patients with otherwise unexplained renal failure, even in the context of contrast medium, endovascular procedures or anticoagulant treatments, the finding of other emboli on renal biopsy provides a decisive element for the diagnosis of AERD (Figure 5) (Muhammad, Zhang et al. 2024).

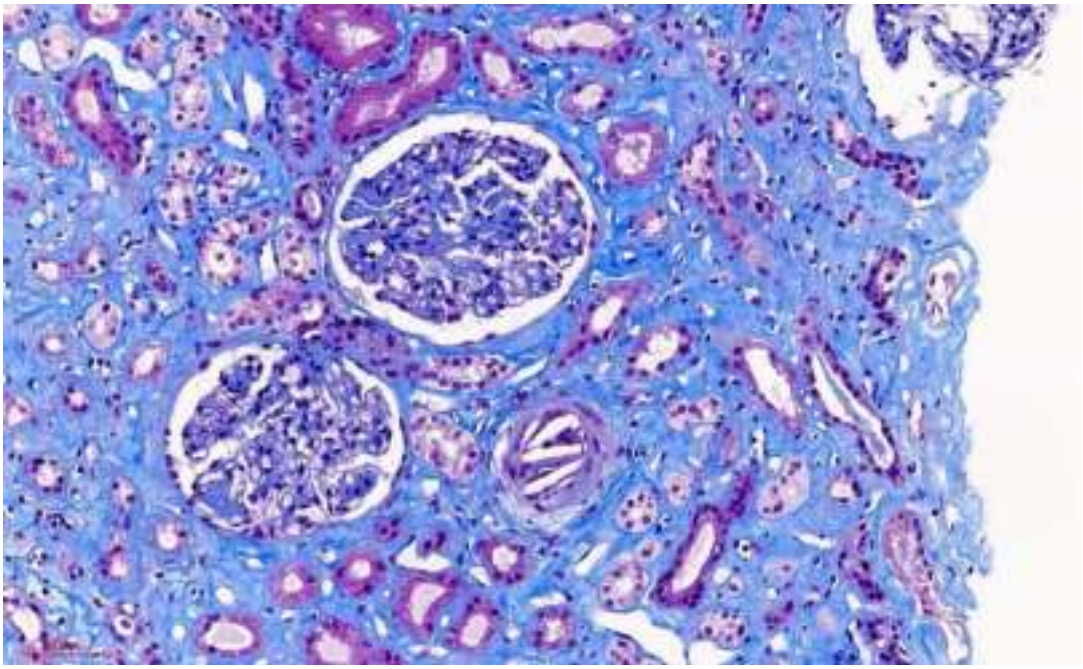

Figure 5: 20x magnification of a slide stained with Masson's trichrome. Two glomeruli with ischemic appearance (increased urinary space, knurled capillary loops) and occluded arteriole due to the presence of cholesterin emboli (courtesy of the Renal Immunopathology laboratory of Parma)

The renal vessels involved in atheroembolism are characterized by the early inflammatory reaction (within 24 hours) with infiltration of polymorphonuclear cells and eosinophils, followed, after 48 hours, by the appearance of macrophages and multinucleated giant cells in the obstructed vessel lumen. Over time, the vessel wall undergoes endothelial proliferation and concentric fibrous thickening of the intima. Focal segmental glomerulosclerosis is possible. Although the etiopathogenic nature is not clear, evidence in the literature suggests an etiopathogenic involvement that concerns both ischemic damage and hyperfiltration damage in non-ischemic nephrons (Murphy 2024).

Prevention and therapeutic protocols

For patients with atheroembolic kidney disease, the main objective is to limit the extent of ischemic damage and prevent the recurrence of new atheroembolic runs. There is no specific therapy, and the therapeutic modalities are mostly preventive and supportive. In patients in whom AERD is recognized, discontinuation of anticoagulant therapy should be considered, and new endovascular procedures should be avoided. In all cases, however, it appears essential to control concomitant risk factors, such as arterial hypertension, heart failure and renal failure. Among the possible therapeutic protocols, the replacement treatment of renal function aimed at managing water overload in patients refractory to high-dose diuretic therapy, controlling acid-base balance and dyslexia cannot be excluded (Sharma, Simon et al. 2024).

Although there are no trials that express the superiority of one dialysis modality over the other, the strategic indication for peritoneal dialysis (in the absence of malnutrition or classic contraindications to treatment) could be effective in attempting to restore renal function, as this method does not require heparin (as usually happens with hemodialysis treatment). However, the rapidity with which

the disease evolves is not permissive in the timing required by peritoneal dialysis. The hemodialysis route often represents an obligatory choice, at least in the acute phase. In these cases, treatment without heparin is more indicated (Arroyo-Andrés, Agud-Dios et al. 2024).

Although the return to *the status quo* of renal function is a target that is difficult to reach, both due to the renal damage that occurs during microembolisms and to concomitant diseases (hypertension, diabetes), there are cases in the literature in which restoration of renal function was achieved after treatment hemodialysis. Kidney damage may be followed by partial recovery of kidney function. In the study presented by Thandani and Camardo, 24% of patients with renal atheroemboli (but without any other complications such as sepsis or hypotension) achieved complete recovery of renal function [6], recovery likely related to multiple factors, such as the resolution of concomitant acute tubular necrosis in ischemic areas, the development of collateral circulation or hypertrophy in the surviving nephrons (Balmforth, Whittington et al. 2024).

Medical therapy is still poorly codified. At the state of the art, no controlled studies have been published that express a unified opinion on the beneficial role of any drug in the treatment of AERD. There has been growing interest in the potential protective role of statins, as occasional cases of other embolic kidney disease have responded to them. Woolson and colleagues, in a predictive study, enrolled 12 patients on statin therapy, demonstrating that they had a reduced risk of developing end-stage AERD. Prospective studies with larger sample sizes confirmed this result and reported that statins have a protective effect even when therapy is started after the diagnosis of other embolic renal disease. This protective effect could be attributable to plaque stabilization and regression through lipid-lowering and anti-inflammatory mechanisms. Plaque stabilization could also reduce the risk of further embolization (GOUDA, DAS et al. 2024).

The use of alirocumab, a completely human monoclonal antibody belonging to the class proprotein convertase subtilisin-kexin type 9 inhibitors (inhibitors of proprotein convertase subtilisin/Kexin type 9, PCSK9). PCSK9 is a protein that regulates circulating LDL cholesterol levels as it binds to LDL receptors, causing their degradation. This results in fewer receptors and higher levels of LDL in circulation. Thanks to its innovative mechanism of action, alirocumab binds to the PCSK9 protein, increases the number of LDL receptors and therefore reduces circulating LDL cholesterol (LDL-C), proving its effectiveness in reducing cardiovascular events, as highlighted by the ODYSSEY OUTCOMES trials and FOURIER (Jayanatha, Kumar et al. 2024).

Another drug that is gaining acceptance (CLEAR Harmony, CLEAR Wisdom trials) is bempedoic acid, an inhibitor of adenosine triphosphate citrate lyase, an enzyme upstream of 3-hydroxy 3methylglutarly-CoA reductase (the target of statins) in the cholesterol biosynthesis. Despite the use of these classes of lipid-lowering drugs, their effectiveness in the management or prevention of AERD has not been studied; the limitations in the use of this class of drug also concern the poor handling experience in cases of impaired renal function (Jin, Chen et al. 2024).

The choice of glucocorticoids appears controversial. Belenfant et al., in a study conducted on 67 patients with AERD (65 males and two females) treated with supportive therapy (prevention of recurrent embolizations, diuretic and cardiological support of heart failure, dialysis support), demonstrated a mortality of 23 % at one year. According to the authors, the administration of low doses of steroids (0.3 mg/kg administered in only 28% of cases) in these patients was associated with favourable effects on mesenteric ischemia, with improvement in abdominal symptoms and rapid resumption of feeding orally. Superimposable appears the experience reported by Stabellini et al. derived from the study of a group of seven patients with AERD, skin lesions, *livedo reticularis* and toe necrosis occurring after coronary arteriography and PT

Discussion

At the patient's bedside, the doctor examines a plethora of pathological conditions capable of justifying the patient's problem, be it acute or chronic. Among these, the AERD hypothesis is only rarely considered. In 2000, Haas and collaborators published the results of a seven-year observational study. A total of 1065 of the 4264 biopsy specimens (25%) analyzed by the authors

were from patients aged 60 years or older, and acute renal failure was the indication for renal biopsy in 259 of these patients (24.3%). The most frequent primary diagnoses on these latest biopsy samples were found to be: pauci-immune crescentic glomerulonephritis with or without arteritis (31.2%); acute interstitial nephritis (18.6%); acute tubular necrosis with nephrotic syndrome (7.5%); AERD (7.1%); acute tubular necrosis in the absence of nephrotic syndrome (6.7%); light chain nephropathy (5.9%); post-infectious glomerulonephritis (5.5%); nephritis due to anti-glomerular basement membrane antibodies (4%); nephropathy due to mesangial deposits of IgA or Henoch Schönlein nephritis (3.6%). Eight biopsy specimens (3.2%) showed only benign nephrosclerosis without an apparent cause of acute renal failure, and another six specimens were found to be inadequate (Kawai, Finn et al. 2024).

Although the study by Haas et al. has demonstrated a greater frequency of AERD compared to other pathologies better rooted in the differential algorithms (such for example, IgA nephropathy, light chain disease, post-infectious glomerulonephritis or anti-glomerular basement membrane antibodies). Despite the evidence just reported demonstrating that AERD is far from absent from the routine clinical scenario, the problem of delayed diagnosis and underestimation of the incidence of AERD remains to date, with some exceptions due to the experience of each centre (Muhammad, Zhang et al. 2024).

In daily clinical practice, it is common experience that the first diagnostic hypothesis, in the context of endovascular interventions resulting in worsening renal function, remains mainly linked to contrast medium damage. In recent years, there has been a redefinition of acute renal damage resulting from the contrast medium and a greater sensitivity among the scientific societies involved to express or not the potential causal link between the infusion of the contrast medium and the appearance of acute kidney injury. For this reason, the definition of Contrast-Associated AKI (CA-AKI), or the synonym post-contrast AKI, has now become common to indicate acute kidney injury (increase in creatinine or decrease in the rate of estimated glomerular filtration rate, eGFR) that occurs shortly after contrast administration and refers to situations in which a detailed clinical evaluation for other potential etiologies of AKI has not been performed or in which different causes of AKI can reasonably be excluded (Murphy 2024).

The Contrast-Induced AKI (CI-AKI) definition, which has replaced the more obsolete one of contrast-induced nephropathy (CIN), refers, however, to an identifiable clinical correlation between contrast medium infusion and AKI in a context where no other possible causes of damage other than exposure to the contrast medium are identified. This attention to contrast medium comparisons is reflected both in the company protocols for preventing the risk of CI-AKI and in the guidelines of the various scientific societies. The 2012 KDIGO guidelines dedicate a large section to the definition of CI-AKI, to the screening of predisposing factors in patients at risk, to prevention and treatment, emphasizing reducing the use of hemodialysis in the absence of overhydration, hyperkalemia or dystonia *to life (Sharma, Simon et al. 2024).*

The radiological guidelines of the European Society of Urogenital Radiology (ESUR) also deal extensively with the risk linked to CI-AKI and the potential complications, also related to extrarenal manifestations, as a consequence of the infusion of contrast medium [88]. However, as clarifying as the position of both scientific societies regards the position of intermittent hemodialysis and hemofiltration in the prevention of CI-AKI, there is no reference to the potential onset of evolutionary renal damage from microembolization. Vascular surgery, on the other hand, provides ample space for atheroembolic problems as a direct (trauma) or indirect (use of oral anticoagulants) complication of endovascular interventions while remaining limited to the possibility of atheroembolic ischemic complications related to the limbs. Only in isolated cases, some authors have postulated the chance of organ damage (e.g., renal) as a consequence of other embolic debris secondary to a renal artery revascularization procedure (Jayanatha, Kumar et al. 2024).

In a combined effort, the Italian Society of Vascular and Endovascular Surgery (SICVE) and the Italian Society of Vascular Angiology and Pathology (SIAPAV) have implemented their guidelines for the diagnosis and therapy of post-procedural ischemic complications, as well as systemic

vasculitis, carrying out a systematic review of the literature and evidence available as of 2015, to support vascular surgeons and radiologists in their decisions on good daily clinical practice. In particular, this joint inter-company effort aims to direct the clinical vascular surgeon and angiologist in selecting the best management and treatment strategy for each patient, taking into consideration both the final result and the risk-benefit ratio of each specific diagnostic assessment and treatment (GOUDA, DAS et al. 2024).

Even in this context, however, AERD remains excluded and once again, the patient (and to a large extent also the doctor who carries out an endovascular examination) finds himself defenceless and unprepared for damage not linked to the chemical properties of the contrast but a direct consequence of a mechanical action of crushing the atheroembolic plaque. Furthermore, to aggravate the problem of not perceiving the risk of post-procedural AERD, routine monitoring for worsening renal function is not performed (Balmforth, Whittington et al. 2024).

Conclusions

Especially in the contemporary context in which the increase in average age, the strengthening of anticoagulation therapy and the growth of vascular interventionism represent excellent conditions for the onset of AERD, an inter-society collaboration involving the different professional figures, such as nephrologists, interventional radiologists, interventional cardiologist and vascular surgeon, for the drafting of shared guidelines (Arroyo-Andrés, Agud-Dios et al. 2024).

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