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Cholesterol Embolization Syndrome After Kidney Transplantation: A Case Series and Systematic Review

Marith I. Francke, BSc,[1,2] Marian C. Clahsen-van Groningen, MD, PhD,[2,3] Thierry P. P. van den Bosch, PhD,[2,3] Jan U. Becker, MD, PhD,[4] and Dennis A. Hesselink, MD, PhD[1,2]

Background. Cholesterol embolization syndrome (CES) is an uncommon but well-known cause of renal failure in native kidneys, but little is known about CES in kidney transplant recipients. The aim of this study was to determine the incidence, clinical characteristics, histopathology, and prognosis of CES after kidney transplantation. **Methods.** CES cases in both transplanted and native kidneys (control group) were identified by searching the databases of the divisions of Nephrology and Pathology of our institution. Clinical data were retrospectively collected. Biopsies were classified according to the latest Banff 2019 Update. Second, a systematic literature search was performed (December 01, 2020) of Ovid MEDLINE, EMBASE, the Cochrane Central Register of controlled trials, Google Scholar, and Web of Science. **Results.** CES was observed in for-cause biopsies of 11 out of 2350 (0.47%) kidney transplant recipients transplanted between January 1, 2006, and December 31, 2018 (0.0009 cases per person-year). All patients had ≥1 cardiovascular risk factor, and 9 donors were expanded criteria donors. Graft loss occurred in 27.3% of the patients diagnosed with CES. Eight transplant biopsies with CES were also classified as biopsy-proven acute rejection. Transplant biopsies showed signs of inflammation (arteritis, n = 7; interstitial inflammation, n = 5; tubulitis, n = 7). One patient with CES in a native kidney was identified. The biopsy of the native kidney only showed arteritis and classified as an isolated "v" lesion. The literature search resulted in 188 unique articles of which 20 were included. A total of 47 cases of CES after kidney transplantation was reported. Cholesterol emboli were found in <1% of all kidney transplant biopsies. In 57.8% of the kidney transplant biopsies with CES described in literature, concomitant inflammation was present. **Conclusions.** CES is an uncommon cause of kidney transplant failure, although the incidence of CES may be underestimated. CES may mimic rejection as it can be accompanied by arteritis.

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INTRODUCTION

Cholesterol embolization syndrome (CES) is an uncommon cause of renal failure.[1–3] Occlusion of renal arteries, arterioles, and glomeruli by cholesterol crystals leads to irreversible ischemic damage and loss of kidney function. CES carries a poor prognosis. It results in the need for dialysis treatment in as much as 37% to 61% of affected patients and has a high mortality rate.[1–4] CES can occur spontaneously or after a triggering event, such as angiography or angioplasty (with or without stent placement), a vascular operation, trauma, or therapy with anticoagulants. The incidence of CES after a vascular intervention ranges between 0.6% and 2.4%, depending on the characteristics of the population studied and the diagnostic

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[1] *Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.*

[2] *Erasmus MC Transplant Institute, Rotterdam, the Netherlands.*

[3] *Department of Pathology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.*

[4] *Department of Pathology, University Hospital of Cologne, Cologne, Germany.*

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Correspondence: Marith I. Francke, BSc, Department of Internal Medicine, Division of Nephrology & Transplantation, Erasmus MC, University Medical Center Rotterdam, Room Rg-527, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. (m.francke@erasmusmc.nl).

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criteria used.[2–4] Especially, cardiovascular compromised patients are at risk for CES. Anticoagulant therapy is also considered a risk factor, as this treatment may lead to the disruption of aortic plaques.[3,5,6]

CES rarely occurs in kidney transplants. Little is known about its incidence, histopathology and prognosis in kidney transplant recipients.[7,8] With the increasing use of expanded criteria donors (ECDs) and increasing numbers of elderly patients receiving transplants,[9,10] CES may become a more important cause of kidney transplant function loss and transplant failure.[11]

Importantly, CES may be underdiagnosed by conventional light microscopy. Cholesterol crystals dissolve during preparation for histological assessment. The classic histological characteristic of CES is the intraluminal presence of rhomboid, in transversal sections needle-shaped clefts (so-called "ghosts") with or without dislodged atheromatous debris. These clefts can be missed in a biopsy due to sampling error. CES can be accompanied by perivascular, intraluminal, or interstitial inflammation with infiltration of lymphocytes, macrophages, mast cells, and eosinophils.[12–18] This inflammation can make it difficult to distinguish whether CES or vascular rejection is the cause of the loss of function of a kidney transplant. Although histological similarities between CES in native kidneys and renal vasculitis have been described,[12,13,19] there are no studies which systematically investigated CES-associated vascular inflammation in kidney transplants.

The aim of this study was to determine the incidence, clinical characteristics, histopathology, and prognosis of CES after kidney transplantation. This was done by studying patients with CES from our center and by performing a systematic search and review of the existing literature.

MATERIALS AND METHODS

Case Series

Renal CES was defined as the presence of at least 1 cholesterol embolus in a renal vessel identified by conventional light microscopy in a kidney core biopsy. All patients with a histologically confirmed diagnosis of CES in either native or transplanted kidneys between January 1, 2006, and December 31, 2018, in the Erasmus MC, University Medical Center Rotterdam, were included in this study. Cases were identified by searching the clinical database of the division of Nephrology and Transplantation, as well as the database, including all biopsy reports, of the department of Pathology, for keywords that could indicate a CES case. Besides CES cases in kidney transplants, CES cases in native kidneys were also included to be able to compare histopathologic findings to those in kidney transplants. The exact number of kidney biopsies performed in kidney transplant recipients during the study period was determined using the Pathology database.

Clinical data were collected from these databases and from the electronic patient files. Follow-up ended on May 1, 2020. Data on risk factors for CES were collected, which included the presence of cardiovascular disease, diabetes mellitus, dyslipidemia, hypertension, peripheral arterial disease, and the use of a vitamin K antagonist. Cardiovascular disease was defined as a medical history of angina pectoris, a coronary artery bypass graft (CABG), myocardial infarction, percutaneous coronary intervention, or stroke. Possible triggering factors of CES were registered, which included the kidney transplantation itself, percutaneous transluminal angioplasty (PTA), aortic catheterization, CABG, thrombolysis, and the start of a vitamin K antagonist, heparin, or factor X antagonists. An ECD was defined as a deceased donor ≥60 years old, or as a donor of 50–59 years old with a history of hypertension, a poor kidney function (>1.5 mg/dL; ie, 133 µmol/L) or a cerebrovascular accident (CVA) as cause of death.

With regard to CES outcome, data were collected on patient survival, graft survival (ending whenever a patient was retransplanted or restarted dialysis—whichever occurred first), and kidney function (serum creatinine concentration and eGFR estimated by the CKD-EPI formula measured at the time of the biopsy and 12 mo after the biopsy). Primary nonfunction was defined as a kidney allograft without function from the moment of transplantation, necessitating dialysis treatment. The incidence of CES was calculated as the number of cases per person-year at risk for CES. A Kaplan-Meier analysis was performed to evaluate the patient survival after CES diagnosis. To evaluate whether the timing of CES affected transplant outcomes, CES occurring within the first posttransplant year was classified as early CES, whereas CES occurring after the first posttransplant year was classified as late CES, as proposed by Lai et al.[7]

All biopsies, from both transplanted and native kidneys, were reviewed by an experienced renal pathologist (MC-vG) and graded according to the updated Banff classification (2019) for kidney transplant biopsies.[20,21]

Literature Review

On December 1, 2020, a systematic literature search was performed of EMBASE, MEDLINE, the Cochrane Central Register of controlled trials, Google Scholar, and Web of Science. The search terms included "cholesterol embolization syndrome" and "kidney transplantation" (see File S1, SDC, http://links.lww.com/TXD/A329, for the search strategy). An article was eligible for inclusion in this systematic review if it was a full-length paper published in English and if at least 1 case of CES in a kidney transplant was reported. Articles neither available at our institution nor available on another online database were excluded. The titles and abstracts of the articles were screened first by 2 independent researchers (M.I.F. and D.A.H.), followed by screening of the full text.

The outcomes of interest were the incidence and prognosis of CES after kidney transplantation, and the pathological findings and the similarities between CES and vascular rejection. Therefore, information on the incidence of CES in kidney transplant recipients and both clinical data (including the type and characteristics of CES, and patient and graft survival) and pathological data of kidney transplant recipients with CES were collected. To summarize the frequency of graft and patient survival, numbers of graft loss and patient deaths were combined and were reported as proportion of the total number of cases included in the articles.

RESULTS

Between January 1, 2006, and December 31, 2018, 2350 patients received a kidney transplant and approximately 1977 kidney transplant biopsies were performed at the Erasmus MC. CES was diagnosed in a for-cause biopsy of 11 kidney transplant recipients, which corresponds with 0.47% of all kidney transplant recipients transplanted, and 0.56% of all

kidney transplant biopsies, during this 12-year study period. The total number of person-years at risk for CES was 12 577. This gives an incidence among kidney transplant recipients of 0.0009 cases of CES per person-year. In the same time period, only 1 case of CES was diagnosed in a native kidney.

Patient Characteristics

Tables 1 and 2 show the characteristics of the 11 kidney transplant recipients diagnosed with CES. Ten patients (90.9%) were male. The median age at the time of CES diagnosis was 69.0 years (IQR, 62.0–74.5). The most common primary kidney disease was hypertensive nephropathy (45.5%; either hypertension alone or in combination with diabetes mellitus or acute kidney injury following aortic prosthesis). The median time on dialysis before transplantation was 18.5 months (IQR, 10.8–24.8).

Five patients received a kidney from either a deceased after circulatory death (DCD; n = 3; 27.3%) or a deceased after brain death (DBD) donor (n = 2; 18.2%). Five donors (81.8%) were classified as ECD. The donors had a median age of 66.0 (IQR, 57.0–70.5) years. Three donors (27.3%) had cardiovascular comorbidities. One donor had a CVA in his medical history, 1 donor smoked and had hypertension, and 1 donor had a myocardial infarction and a PTA of the aortic bifurcation.

Hyper-eosinophilia in the peripheral blood was not observed in any of the patients at the time of CES diagnosis.

TABLE 1.

Patient characteristics (n = 11)

Sex	
Male	10 (91%)
Female	1 (9%)
Primary kidney disease	
Hypertensive nephropathy[a]	5 (45%)
Cholesterol embolization syndrome + diabetic nephropathy	1 (9%)
Focal segmental glomerulosclerosis	1 (9%)
Obstructive nephropathy	1 (9%)
Polycystic kidney disease	2 (18%)
Unknown	1 (9%)
Renal replacement therapy before transplantation	
Hemodialysis	4 (36%)
Peritoneal dialysis	4 (36%)
Pre-emptive transplantation	3 (27%)
Median age at kidney transplantation (y)	69.0 (IQR, 62.0–70.0)
Median donor age at kidney transplantation (y)	66.0 (IQR, 57.0–70.5)
Type of donor	
Deceased after brain death	2 (18%)
Deceased after circulatory death	3 (27%)
Living related	2 (18%)
Living unrelated	4 (36%)
Expanded criteria donor	9 (82%)
Median age at CES diagnosis (y)	67 (IQR, 60.5–73.0)
Type CES	
Early (<1 y after kidney transplantation)	7 (64%)
Late (>1 y after kidney transplantation)	4 (36%)
(Cardiovascular) comorbidities	
Cardiovascular disease (CABG/MI/PCI/stroke)	8 (73%)
Diabetes mellitus	5 (45%)
Dyslipidemia	8 (73%)
Hypertension	11 (100%)
Peripheral arterial disease (PTA/stent)	3 (27%)

[a]The cause of end-stage renal disease was in one patient a combination of hypertensive nephropathy and the placement of an aortic prosthesis and in another patient a combination of hypertensive and diabetic nephropathy.

AKI, acute kidney injury; CABG, coronary artery bypass graft; CES, cholesterol embolization syndrome; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.

Timing, Triggers, and Treatment of CES

Table 3 shows the timing, triggers, and treatment of CES in each kidney transplant recipient. In 7 cases (63.6%), CES was diagnosed within 1 year after kidney transplantation (early CES). In the remaining 4 cases (36.4%), CES occurred >1 year after kidney transplantation (late CES). Based on the timing of CES and the lack of other possible triggers, the trigger may have been the kidney transplantation itself in 6 cases (54.5%), in particular the arterial anastomosis and clamping of the iliac artery. In 1 early case, CES was most likely triggered by CABG performed approximately 1 month before the CES diagnosis. In the 4 cases of late CES, factors that may have triggered CES were CABG (n = 1; 9.1%), PTA (n = 1), and the start of treatment with a vitamin K antagonist (n = 1). In one case, no possible trigger could be identified.

In 3 cases (27.3%), no specific treatment for CES was initiated. In 8 cases, therapy was initiated. When treated, the most common approach was the start or the adjustment of lipid-lowering therapy (n = 3; 27.3%). In 2 patients (18.2%), therapy consisted of (tighter) blood pressure and diabetes mellitus control. In 1 of the 4 patients who used vitamin K antagonists before the CES diagnosis, the vitamin K antagonist was withdrawn and the patient's statin dose was increased. In 2 cases (18.2%), methylprednisolone pulse therapy was initiated (before the biopsy was performed), because of suspected acute rejection.

Clinical Outcomes

In total, 4 out of 11 patients died during the follow-up period (Table 3). One of these patients died within a year after CES diagnosis due to a ruptured thoracic aneurysm. The other 3 patients died at least 1 year after CES was diagnosed. The causes of death were renal failure due to diabetic nephropathy and CES, pneumonia with renal failure and cardiac arrhythmia, and upper gastro-intestinal bleeding with hemorrhagic shock. Figure S1 (SDC, http://links.lww.com/TXD/A329) shows the Kaplan-Meier survival estimates after CES diagnosis.

The kidney function of the patients at the time of biopsy and 1 year after the biopsy are shown in Table 3. In 3 CES cases graft loss occurred. All 3 patients who lost their graft, already restarted dialysis before a kidney biopsy was performed. One kidney allograft never functioned and was classified as primary nonfunction. Two kidney transplant recipients with a functioning graft posttransplantation, developed kidney failure and restarted dialysis a month before and at the time of CES diagnosis.

Patient and graft survival were stratified for early and late CES. During the studied period, 3 patients with early CES died (42.9%; including the patient that died within the first year after CES diagnosis) and 1 patient with late CES died (25%). Graft loss occurred in 2 out of 7 (28.6%) early CES cases and in 1 out of 4 (25%) late CES cases.

Pathology Findings

One patient with CES in a native kidney was identified. This patient was a 68-year-old male, who suffered from

TABLE 2.

Individual patient and donor characteristics

			Kidney transplant recipient				Kidney transplant donor					
	Early/late CES	Trigger	Sex (M/F)	Age	Primary kidney disease	Cardiovascular comorbidities	Donor type	Sex (M/F)	Age	Cause of death	Cardiovascular risk factors	ECD (Y/N)
KT-1	Late	Start Vitamin K antagonist	M	77	Hypertensive and diabetic nephropathy	CVA Diabetes Dyslipidemia Hypertension	DCD	M	67	Trauma. Subdural hematoma	None	Y
KT-2	Early	KTx	M	44	Polycystic kidney disease	AP MI Hypertension	LUR	M	68	–	None	N
KT-3	Late	CABG	M	75	Hypertensive nephropathy	CABG MI CVA Dyslipidemia Hypertension	LUR	F	73	–	None	N
KT-4	Early	KTx	M	69	Hypertensive nephropathy	Hypertension PAD	LUR	M	66	–	None	N
KT-5	Late	none	M	80	Hypertensive nephropathy in combination with acute kidney injury after the placement of an aortic prosthesis	Aortic prothesis Diabetes Dyslipidemia Hypertension	LR	M	35	–	None	N
KT-6	Early	KTx	M	61	CES and diabetic nephropathy	AP CABG PCI Diabetes Dyslipidemia Hypertension PAD	LR	F	39	–	None	N
KT-7	Early	KTx	F	72	Polycystic kidney disease	Diabetes Dyslipidemia Hypertension	DCD	M	64	Out of hospital cardiac arrest	Smoking PTA Aortic bifurcation MI	Y
KT-8	Early	KTx	M	67	Unknown	CABG Dyslipidemia Hypertension	DCD	M	76	CVA	CVA	Y
KT-9	Early	CABG	M	63	Focal segmental glomerulosclerosis	CABG Dyslipidemia Hypertension	LUR	F	60	–	None	N
KT-10	Late	PTA	M	74	Acquired obstructive nephropathy. Atherosclerosis	CABG CVA MI PTA Diabetes Dyslipidemia Hypertension	DBD	F	73	Subarachnoid hemorrhage	None	Y
KT-11	Early	KTx	M	46	Hypertensive nephropathy	Hypertension	DBD	F	54	Subarachnoid hemorrhage	Smoking Hypertension	Y

AP, angina pectoris; CABG, coronary artery bypass graft; CES, cholesterol embolization syndrome; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; ECD, expanded criteria donor; KT, kidney transplant recipient; KTx, kidney transplantation; LR, living related; LUR, living unrelated; MI, myocardial infarction; PAD peripheral arterial disease; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.

hypertension, was previously treated with PTA, and diagnosed with a CVA. All 12 kidney biopsies in which cholesterol embolisms were observed, were classified according to the Banff classification (Table 4; Figure 1A and B).[20,21] According to this classification, 7 transplant (64%) biopsies could be classified as acute T cell–mediated rejection (aTCMR) and 1 transplant biopsy (9%) was classified as suspect for antibody-mediated rejection (aAMR).

All 7 transplant biopsies showed mild to moderate arteritis (v1 to v3). In addition, interstitial inflammation (i1-3) and tubulitis (t1-3) was reported in n = 5 and n = 7 transplant biopsies with CES, respectively. One of the 7 transplant biopsies showed an isolated "v" lesion.

The biopsy of the native kidney, if classified according to the Banff classification, would be classified as an aTCMR due to the presence of an isolated "v" lesion (v1). Neither interstitial inflammation nor tubulitis was observed in this native kidney biopsy.

Literature Review

The search revealed 268 articles and after removal of duplicates, 188 articles were screened for eligibility. After

TABLE 3.

Clinical outcomes

	Year of KTx	Year of CES diagnosis	Days KTx-CES	Clinical presentation	Trigger	Treatment	T = biopsy		T = 12 mo		Transplant survival (days after KTx, biopsy)	Patient survival	Cause of death
							Creatinine	eGFR	Creatinine	eGFR			
KT-1	2007	2014	2673	Deterioration of kidney function	Start Vitamin K antagonist	Before the biopsy: Methylprednisolone (3 d) and start hemodialysis After the biopsy: dose reduction immunosuppression	Dialysis		Dialysis		2669, 0	NA	NA
KT-2	2009	2010	61	Deterioration of kidney function	KTx	Start pravastatin	223	30	233	28	NA	NA	NA
KT-3	2009	2014	1789	Deterioration of kidney function	CABG	Switch from pravastatin to atorvastatin	190	29	–	–	NA	NA	NA
KT-4	2008	2009	142	Deterioration kidney function	KTx	Methylprednisolone (no effect)	252	22	Death		NA	170, 28	Ruptured thoracic aneurysm
KT-5	2007	2017	3697	Deterioration kidney function	None	None	107	56	105	58	NA	NA	NA
KT-6	2005	2006	26	Fever, pain kidney allograft, deterioration kidney function	KTx	Before the biopsy: Methylprednisolone (3 d) After the biopsy: Stop marcoumar. Blood pressure and diabetes control	363	15	261	22	NA	3261, 3235	Renal failure due to diabetic nephropathy and CES, stop hemodialysis
KT-7	2012	2012	89	Primary nonfunction, fever, retroperitoneal abscess	KTx	Antibiotics Transplant nephrectomy	Dialysis		Transplantectomy		0, 0	NA	NA
KT-8	2014	2015	192	Deterioration of kidney function	KTx	Rouvastatine	193	30	–	–	NA	NA	NA
KT-9	2007	2007	34	Deterioration kidney function	CABG	None	Dialysis		Dialysis		7, 0	650, 616	Pneumonia with renal failure and cardiac arrhythmia
KT-10	2010	2013	1080	Deterioration of kidney function	PTA	Stop vitamin K antagonist Start carbasalaatcalcium Increase of statin dose	185	30	–	–	NA	1753, 673	Upper gastrointestinal bleeding
KT-11	2018	2018	23	Stagnation recovery kidney function after KTx	KTx	Blood pressure and diabetes control	201	33	233	28	NA	NA	NA

CABG, coronary artery bypass graft; CES, cholesterol embolization syndrome; eGFR, estimated glomerular filtration rate; KT, kidney transplant recipient; KTx, kidney transplantation; NA, not available; PTA, percutaneous transluminal angioplasty.

TABLE 4.

Banff classifications kidney biopsies

	i	t	v	g	ptc	ci	ct	cv	cg	mm	ah	ti	i-IFTA	C4d	Isolated "v" lesion	Treatment
KT-1	0	0	1	0	0	3	3	1	0	0	2	3	3	2	Yes	Before the biopsy: Methylprednisolone (3 d) and start hemodialysis After the biopsy: dose reduction immunosuppression
KT-2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No	Start pravastatin
KT-3	1	1	1	0	1	2	2	2	0	0	0	2	1	0	No	Switch from pravastatin to atorvastatin
KT-4	0	2	0	0	1	2	1	1	0	0	1	2	2	0	No	Methylprednisolone (no effect)
KT-5	0	0	0	0	0	1	1	0	0	0	0	2	1	0	No	None
KT-6	3	3	3	3	3	0	0	2	0	0	0	0	0	np	No	Before the biopsy: Methylprednisolone (3 d) After the biopsy: Stop marcoumar. Blood pressure and diabetes control
KT-7	2	1	2	3	2	0	1	1	0	0	0	2	0	0	No	Antibiotics Transplant nephrectomy
KT-8	1	2	2	0	0	1	1	1	0	0	0	2	2	0	No	Rouvastatine
KT-9	1	1	1	2	0	1	1	1	0	0	0	0	0	0	No	None
KT-10	0	1	1	1	0	1	1	1	0	0	0	1	1	0	No	Stop vitamin K antagonist Start carbasalaatcalcium Increase of statin dose
KT-11	0	0	0	0	0	1	1	1	0	1	2	1	1	0	No	Blood pressure and diabetes control.
Nat-1	0	0	1	3	0	1	1	0	0	0	0	1	1	np	Yes	Blood pressure control

ah, arteriolar hyalinosis; cg, glomerular basement membrane double contours; ci, interstitial fibrosis; ct, tubular atrophy; cv, vascular fibrous intimal thickening; g, glomerulitis; i, interstitial inflammation; i-IFTA, inflammation in the area of IFTA; IFTA, interstitial fibrosis and tubular atrophy; KT, kidney transplant; mm, mesangial matrix expansion; Nat, native kidney; ptc, peritubular capilaritis; t, tubulitis; ti total inflammation; v, arteritis.

screening based on title and abstract, a total of 135 articles were excluded (no English article, n = 5; not reporting on CES in a kidney transplant, n = 130). Of the remaining 53 articles, 33 were excluded based on the full text (absence of full text, n = 7; not reporting on CES in a kidney transplant, n = 26) and 20 were included in this literature review (Figure 2). Out of the 7 articles without available full text, 3 were published between 1986 and 1996 and were not available online. The other 4 articles were abstracts of conference meetings and as these did not consist of full text they did not meet our inclusion criteria.

Incidence of CES After Kidney Transplantation

The literature revealed 20 articles, describing a total of 47 cases of CES after kidney transplantation (Table 5). Only 3 studies reported on the incidence of CES after kidney transplantation. Lai et al[7] reported an incidence of 0.39% among kidney transplant recipients. They found cholesterol embolisms in 21 biopsies (of 14 patients) out of a total of 5435 kidney allograft biopsies. A CES incidence of 0.47% was reported by Ripple et al.[8] Out of a total of 1500 kidney transplant biopsies, 7 biopsies (of 7 different patients) were diagnostic for CES. Koch et al[22] reported kidney allograft loss, caused by CES in 2 out of 429 kidney transplant recipients (0.5%).

Prognosis

Kidney transplant loss occurred in 21 out of the 45 cases (46.7%) described in literature.[7,8,14–16,22,23,25,27–31,33] However, in at least 6 of these cases (13.3%), transplant loss was probably not caused by CES.[7,28,33] In studies that described >2 CES cases (ie, after the exclusion of case reports), 7 out of 23 grafts failed (30.4%).[7,8,30] In 3 of these 7 cases, CES alone was most likely the reason of graft failure.

The source of the cholesterol embolus can be either the donor or the recipient and the prognosis of CES might differ between donor and recipient-derived CES. The determination of the origin of the cholesterol emboli is based on clinical judgement. Lai et al[7] found significantly more CES-specific graft loss in donor-derived CES compared with recipient-derived CES when looking at all cases (53.5% versus 9.1%, respectively; $P = 0.00459$), which might also be due to the detrimental effect of concurrent chronic hypertensive, diabetic, or atheromatous kidney damage from the donor. Also, the timing of CES has been associated with prognosis. Graft loss was

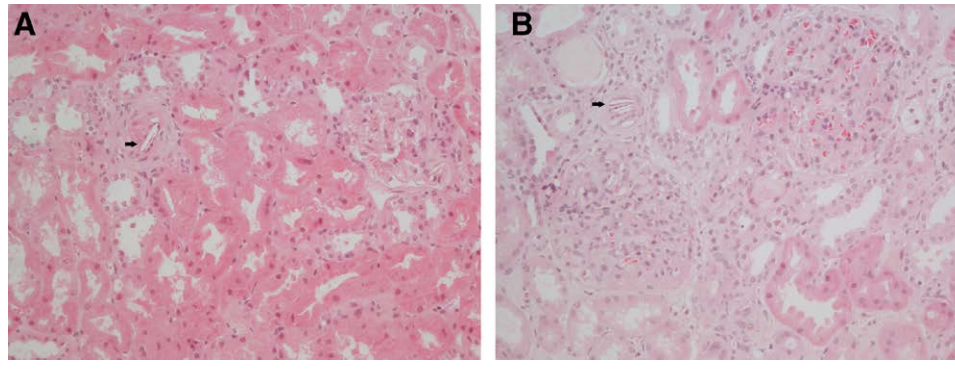

FIGURE 1. Cholesterol emboli in a kidney transplant (A) and a native kidney (B).

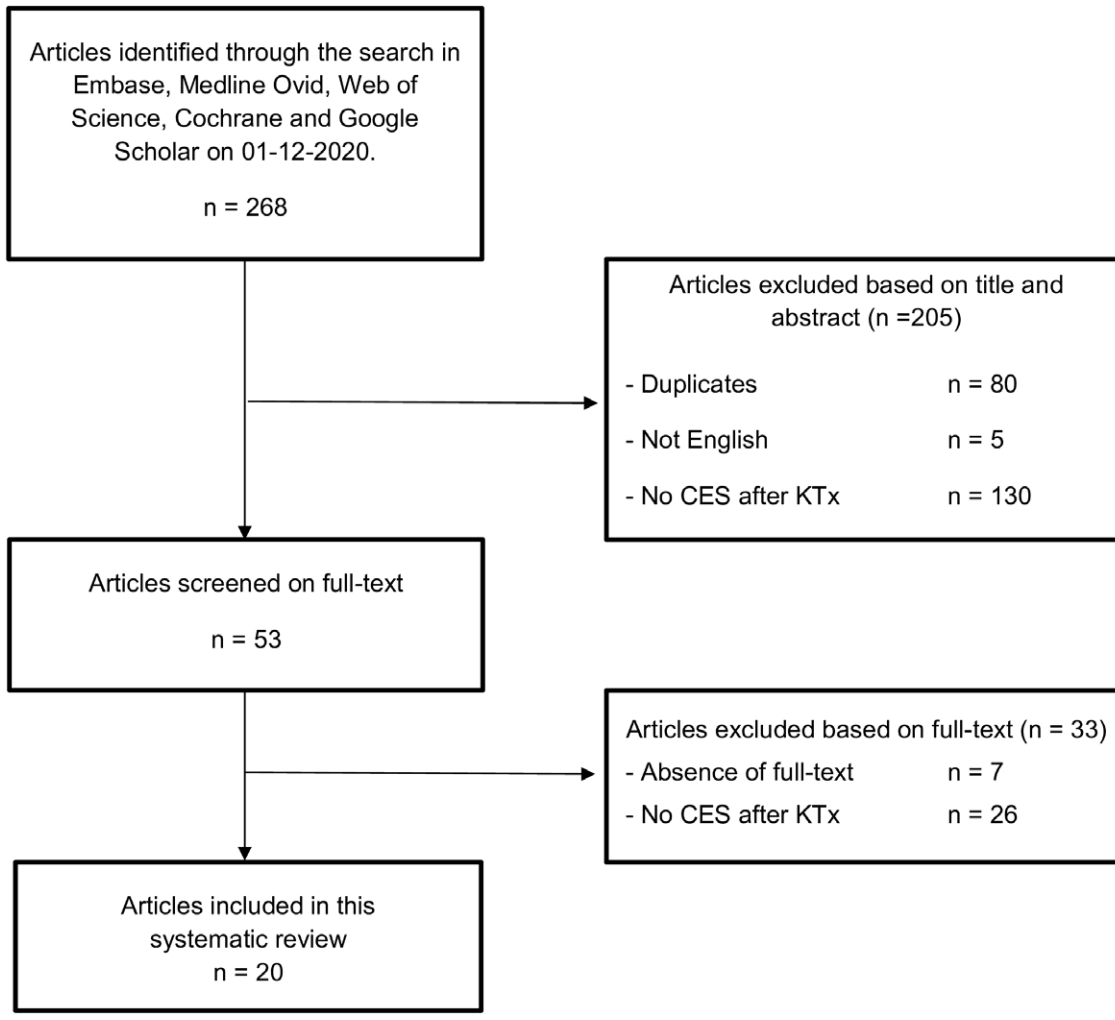

FIGURE 2. Flowchart of the study selection. CES, cholesterol embolization syndrome; KTx, kidney transplantation.

reported in 40% of the early CES cases (n = 25), whereas no graft loss was reported in the 12 late CES cases ($P = 0.00938$).[7]

Pathological Findings

Pathology findings are summarized in Table 5. Cholesterol emboli are most commonly found in interlobular arteries[7,16,18,23,24,28,32] and arcuate arteries.[7,16,18,28–30] In 19 biopsies studied by Lai et al,[7] cholesterol emboli were found in interlobular arteries in 14 cases (73.7%) and in arcuate arteries in 2 (10.5%). Concomitant histological findings were tubular atrophy and necrosis,[7,8,15–17,24,26–28,32–34] nephrosclerosis,[8,24] inflammation or cellular infiltrate,[14–18,24,32,33] hyaline changes,[8,23,27] negative C4d staining,[23,24] fibrous intimal thickening,[14,32,33] and interstitial fibrosis (Table 5).[8,27]

None of the articles investigated histological similarities between CES and vascular type rejection in kidney transplants or how to differentiate between these 2 diagnoses. In total, in 26 of the 45 biopsies that showed a cholesterol embolus (57.8%), either rejection or inflammation was reported. (Signs of) vascular type rejection and aTCMR were reported in respectively 4[8,31,34] and 14[7,8,17,23,30,34] biopsies as pathological findings. Lai et al[7] reported 9 cases with borderline changes suspicious for aTCMR. Concurrent chronic rejection was described in 2 biopsies.[28,30] Moreover, multiple studies observed signs of both vascular[14,15,18,24] and tubulo-interstitial[15–17,32] inflammation and cellular infiltrate in the kidney biopsies that was not specifically classified as rejection.

DISCUSSION

CES is an uncommon cause of renal failure in kidney transplant recipients. We report a fair number of CES cases from a large cohort of kidney transplant recipients. CES was diagnosed in 11 of all for-cause biopsies (0.56%) taken during a 13-year time period. This number is in line with numbers from the literature. However, none of the included studies reported the number of cases per person-year, which makes it difficult to compare our results to the literature. Although the incidence that was observed in the present study (0.0009 cases per person-year), may be an underestimation due to the retrospective design of the study and the inclusion of for-cause biopsies only, we believe that clinically significant CES is a rare phenomenon after kidney transplantation.

Kidney transplant recipients with cardiovascular comorbidities are at higher risk for developing CES. In our center, 73% of the CES patients suffered from cardiovascular disease, and all patients either had diabetes mellitus, hypertension, dyslipidemia, or a combination of these. Also, having a donor with cardiovascular morbidity may increase the risk for CES. In the present study, 5 donors fulfilled the criteria for ECDs.

TABLE 5.

CES cases from the literature

Article	CES cases (n = 47)	CES origin		Affected vessels		Coexisting biopsy findings/diagnosis		Prognosis	
González et al[23]	2	Recipient	(2)	Interlobular artery	(2)	Arteriolar hyalinosis	(1)	Graft loss	(2)
						ACR Banff IIA	(1)	- Restart dialysis	
						Negative C4d staining	(1)		
Ahmed et al[15]	1	Recipient	(1)	Arteries	(1)	Chronic transplant nephropathy	(1)	Graft loss	(1)
						Tubular atrophy	(1)	- Restart dialysis	
						Focal infiltrate of mononuclear cells	(1)		
Pliquett et al[24]	2	Donor	(2)	Arterioles	(2)	Macrophages and lymphocytes	(2)	Delayed graft function	(2)
				Interlobular arteries	(2)	Subendothelial C1q deposit	(2)		
						Nephrosclerosis	(2)		
						Tubular injury	(2)		
						Negative C4d and C3 staining	(2)		
Ackoundou-N'Guessan et al[25]	1	Donor	(1)	Arteries	(1)			Graft loss	(1)
								- Retransplantation	
Ott et al[26]	1	Recipient	(1)	Small arteries	(1)	Focal tubular injury	(1)	Delayed graft function	(1)
						Regenerative changes	(1)		
Lai et al[7]	12	Recipient	(9)	Arcuate arteries		ATN	(1)	Recovery	(7)
		Donor	(3)	Interlobular arteries		ACR	(9)	Graft loss	(1)
				Arterioles		Drug-related changes	(2)	- PNF	(1)
				Glomerular capillaries		BKV tubulointersitial nephritis	(1)	- Chronic rejection	(1)
						Chronic allograft nephropathy	(10)	- BKV infection	(1)
								- PNF + ACR	
Schönermarck et al[27]	1	Donor	(1)	Small arteries	(1)	Arteriolohyalinosis	(1)	Graft loss	(1)
						Interstitial fibrosis	(1)	- Restart dialysis	
						Tubular atrophy	(1)		
						ATN	(1)		
						Interstitial fibrosis	(1)		
Scolari et al[28]	2	Recipient	(1)	Interlobular artery	(1)	ATN	(2)	Recovery	(1)
		Donor	(1)	Arcuate arteries	(1)	Chronic rejection	(1)	Graft loss	(1)
								- Renal carcinoma	
Chaudhury et al[29]	1	Donor	(1)	Arcuate arteries + segmental arteries	(1)	Endothelial lining	(1)	Graft loss	(1)
								- Nephrectomy	
Ripple et al[8]	7	Recipient	(6)	Arteriole	(2)	Arteriolohyalinosis	(1)	Recovery	(5)
		Donor	(1)	Small artery	(4)	Sclerotic glomeruli	(1)	Graft loss	(2)
						Mild focal interstitial fibrosis	(2)		
						Mild acute tubular injury	(2)		
						PTLD	(1)		
						Nephrosclerosis	(1)		
						ATN	(1)		
						ACR	(1)		
						Acute vascular rejection	(1)		
						CMV infection	(1)		
Shappell et al[16]	1	Donor	(1)	Interlobular arteries + arcuate arteries + large arteries	(1)	ATN	(1)	Graft loss	(1)
						Neutrophils in glomerular capillary loops	(1)	- Nephrectomy	
						Macrophages + giant cells	(1)		
						Fibrous reaction	(1)		
						Focal subscapular lymphocytic interstitial infiltrate	(1)		
						Intimal fibrosis	(1)		
de Takats et al[30]	4	Recipient	(2)	Arteries	(3)	Necrotic kidney	(1)	Recovery	(3)
		Donor	(2)	Arcuate arteries	(1)	ACR	(1)	Graft loss	(1)
						Chronic rejection	(1)	- Nephrectomy	
Bolander et al[31]	2	Donor	(2)	Arteries + glomerular	(1)	Vascular rejection	(2)	Graft loss	(2)
				small arteries	(1)	Cortical necrosis	(1)	- Nephrectomy	
Singh et al[32]	1	Donor	(1)	Interlobular arteries	(1)	ATN	(1)	Recovery	(1)
				Glomerular	(1)	Interstitial edema	(1)		
						Acute interstitial inflammation	(1)		
						Fibrous intimal thickening	(1)		
Aujla et al[33]	2	Recipient	(1)	Small arteries	(1)	Fibrous intimal thickening	(2)	Recovery	(1)
		Donor	(1)	Arteries	(1)	Glomerulosclerosis	(1)	Graft loss	(1)
						Increase mesangial matrix	(1)	- ACR	
						Increase cellularity	(1)		
						ATN	(1)		

Continued next page

TABLE 5. (Continued)

CES cases from the literature

Article	CES cases (n = 47)	CES origin		Affected vessels		Coexisting biopsy findings/diagnosis		Prognosis	
Bellamy et al[14]	1	Donor	(1)	Segmental arteries + small arteries	(1) (1)	Intimal fibrosis Intraluminal eosinophilic material	(1) (1)	Graft loss - Primary nonfunction	(1)
Corradetti et al[17]	2	Recipient Donor	(1) (1)	Arterioles	(1)	ATN Inflammatory interstitial infiltrate Interstitial edema Borderline cellular rejection	(1) (1) (1) (1)	Recovery	(2)
Renders et al[34]	1	Donor	(1)	Small arteries Arterioles	(1) (1)	ATN Signs interstitial cellular rejection Chronic vascular rejection	(1) (1) (1)		
Pirson et al[18]	1	Recipient	(1)	Arcuate arteries Interlobular arteries Preglomerular arterioles	(1) (1) (1)	Inflammatory reaction, macrophages Fibrosis	(1) (1)		
Koch et al[22]	2							Graft loss	(2)

ACR, acute cellular rejection; ATN, acute tubular necrosis; BKV, BK virus; CES, cholesterol embolization syndrome; CMV, cytomegalovirus; PNF, primary nonfunction; PTLD, posttransplant lymphoproliferative disorder.

We expected the incidence of CES would be increased due to both the increasing numbers of elderly transplanted patients and increasing use of kidneys from ECD donors. However, our case study shows that this is not the case. Although the occurrence of CES is underestimated, CES appears to be a rare diagnosis, even in the current era. We therefore believe that a transplantation should not be withheld from otherwise suitable candidates despite a perceived high risk of (donor-derived) CES.

CES has a poor prognosis, with graft loss reported in 27.3% of the cases in our center. In the literature, graft loss in patients with CES occurred in as much as 46.7% of the cases. The time to graft loss ranged from the day of CES diagnosis to 5 years after the diagnosis. However, the literature revealed mostly case reports, which makes it difficult to estimate the prognosis of CES. Recovery of kidney function was most frequently reported in larger studies.[7,8] This indicates possible reporting bias and an overestimation of the occurrence of graft loss. In the present study, no difference in prognosis between early and late CES was observed. However, according to the literature, early CES carries a poorer prognosis than that of late CES (with graft loss reported in 10 out of 25 versus 0 out of 12 cases, respectively).[7] In addition, donor-derived CES has been associated with a higher incidence of graft loss than recipient-derived CES.[7,8]

The optimal treatment for CES in kidney transplant recipients is unclear. In our case series, treatment mostly consisted of optimal blood pressure-, diabetes mellitus- and lipid control, and sometimes adjustment of vitamin K antagonist therapy or anticoagulation. Although in the literature different treatment strategies have been suggested, to the best of our knowledge, no clinical trials have been performed in kidney transplant recipients. Treatment is mostly preventive and the most common strategy consists of statin therapy.[3,28] This treatment strategy seems reasonable, as statins reduce low-density lipoprotein concentrations, as well as the size and stability of atherosclerotic plaques.[35] The severity of atherosclerosis has been shown to be a risk factor for systemic CES.[36–38] Moreover, statins have an anti-inflammatory effect, which may reduce the inflammatory damage in the early phase after CES.[39] In 95 patients with systemic CES with renal failure (atheroembolic renal disease), the use of statins at baseline was associated with a significantly lower risk to develop end-stage renal disease.[40] Another therapy that has been successful in some CES cases in kidney transplants is the addition of intravenous iloprost (a prostaglandin I2 agonist) to statin and glucocorticoid treatment.[17] Theoretically, this drug might reduce the inflammation and vasoconstriction caused by CES, via its effect on the vessel wall and its effect on cytokine production.[17]

In the present series, 8 out of 11 biopsies of CES cases in kidney transplant recipients, showed signs of rejection and in 2 patients antirejection therapy was administered. In the literature, signs of rejection and inflammation have been frequently reported in kidney transplant biopsies with CES (57.8%).[7,8,14–18,23,24,28,30–32,34] Interestingly, the pathological findings in the native kidney could also be classified as "rejection," because of the presence of isolated arteritis. This observation is in line with the literature, in which an inflammatory reaction around the cholesterol embolus, mostly involving macrophages, eosinophils, and giant-cells, is frequently described.[4,6] These results suggest that CES may mimic an isolated "v" lesion, which according to the current Banff classification should be regarded an aTCMR type 2 rejection. Ideally, histological factors could distinguish between patients with inflammation caused by CES, patients experiencing a rejection episode, and patients suffering from these 2 diagnoses at the same time. Based on our observations and the cases in the literature, the presence of tubulitis or interstitial inflammation might be suggestive of a rejection episode, whereas an isolated "v" lesion may make CES more likely. The performance of protocol biopsies, as well as the comparison of CES in transplant biopsies to CES in native kidney biopsies, may help in confirming this hypothesis and may reveal other factors that allow better distinction between the diagnoses. Making the right diagnosis is important, as this is a vulnerable patient population, in which (potential) unnecessary antirejection therapy can have great implications for clinical outcomes. On the other hand, the poor prognosis of the kidney transplant recipients described here, may have been caused, at least in part, by untreated rejection. However, at this moment, we do

not recommend taking protocol biopsies in kidney transplant patients with a high risk of CES, since there is no evidence-based therapy for (subclinical) CES in this population and a biopsy carries a risk of complications.

A limitation of this study is its retrospective design, which may have resulted in an underestimation of the incidence of CES in kidney transplant recipients, as we may have missed some cases by searching the databases, and some biopsies were not available for histological review. Also, we may have missed subclinical CES cases, as in this study only for-cause biopsies were evaluated. In addition, we were unable to determine the total number of kidney biopsies that were performed in the study period. This could explain the different frequencies in which CES was observed in our study compared with the literature.[7,8] Another limitation is that the number of cases was small. Especially since only 1 case of CES in a native kidney was found, we were not able to find factors that could distinguish CES from rejection. Moreover, the literature revealed mostly case reports, which makes it difficult to estimate the incidence and prognosis of CES.

CONCLUSION

CES is an uncommon diagnosis after kidney transplantation although the incidence may be underestimated. CES after kidney transplantation is often accompanied by histopathologic findings that suggest concurrent type 2 aTCMR. Therefore, both CES and acute rejection should be included in the differential diagnosis of allograft failure, especially in cardiovascular compromised patients or in patients having a cardiovascular compromised donor, who are at higher risk for CES.

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