DOI: 10.20514/2226-6704-2020-10-4-272-280

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Cholesterol Atheroembolism Syndrome: Current State of the Problem

Abstract

Cholesterol atheroembolism syndrome is a systemic pathological process caused by the embolization of small arteries with cholesterol crystals, which can develop spontaneously, and it is the result of intravascular surgery and / or the use of anticoagulants. Embolization cholesterol crystals leads to ischemic and inflammatory organ damage. The clinical picture is variable, various organs can be targets, but skin and kidneys are mainly affected. Specific clinical and laboratory signs aren't. Tissue biopsy is the gold standard for diagnosis cholesterol atheroembolism syndrome. The treatment is based on the correction of classical cardiovascular risk factors, the use of statins. In terms of benefit and risk failure from anticoagulants and thrombolytics should be considered. Studies on the use of corticosteroids, cytostatic, and colchicine have conflicting results. The use of monoclonal antibodies of IL-1 antagonists is a perspective direction.

Key words: *cholesterol-embolization, atherosclerosis, cardiac surgery, acute kidney injury, biopsies, statins*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 18.05.2020

Accepted for publication on 06.07.2020

For citation: Mikhailova Z.D., Klimkin P.F. Cholesterol Atheroembolism Syndrome: Current State of the Problem. The Russian Archives of Internal Medicine. 2020; 10(4): 272-280. DOI: 10.20514/2226-6704-2020-10-4-272-280

AKI — acute kidney injury, ARD — atheroembolic renal disease, CC — cholesterol crystals, CES — cholesterol embolization syndrome, CRP — C-reactive protein, GCS — glucocorticosteroids, IL-1ß — interleukin-1ß

Cholesterol embolization syndrome (CES) is a systemic pathological process caused by embolization of small arterial vessels in the skin, kidneys, retina, gastrointestinal tract and brain with microcrystals of cholesterol atherosclerotic plaques in the aorta and other major arteries, which results in ischemic and inflammatory damage to corresponding organs [1–3].

Previously, CES was detected primarily by pathologists based on autopsy results, and its incidence varied from 0.31 to 8.2% [4]. The incidence of CES was significantly higher (12–77%) in the autopsy of elderly patients who died after aortic surgery or aortography [2]. Clinically significant CES has an incidence of 0.09–2.9% due to widespread intravascular surgeries and the use of anticoagulants and thrombolytic agents. However, in most cases, CES can be easily overlooked. Therefore, its actual incidence is probably much higher [2].

Risk Factors

Atherosclerosis is the most important risk factor for CES. Factors contributing to CES include the causes

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of atherosclerotic plaque instability: inflammation, hemodynamic stress, smoking, dyslipidemia, old age, lack of statin treatment; the effect of anticoagulants and thrombolytics is also under consideration. According to Agrawal A. et al. (2018), who analyzed 24 studies, about 78% of patients with CES had arterial hypertension, 18% had diabetes mellitus, 31% had hyperlipidemia, 60% — coronary heart disease, 58% were smokers, and 79.8% were men [5]. The risk of CES increases in the presence of ulceration in atherosclerotic plaque, thrombus mobility and plaque thickness ≥4 mm [3].

In more than 70% of cases, CES arises after interventional procedures (coronary angiography and aortography), or cardiovascular surgery, about 20% of cases arise spontaneously [6, 7].

Inflammation is an equally important risk factor for CES. The level of C-reactive protein (CRP) in plasma of patients with CES was significantly higher than in patients without CES (2.4 and 0.7 mg/dl, respectively; p = 0.01). Multivariate analysis showed that a high CRP level was an independent predictor of CES (RR 4.6, p = 0.01) [8].

CES was previously associated with anticoagulants and fibrinolytics. It is believed that these drugs lead to the rupture of atherosclerotic plaques, causing internal hemorrhage and breakdown of fibrous capsules [9]. However, without intravascular interventions or surgeries, these drugs rarely lead to CES [10, 11].

According to Agrawal A. et al. (2018), 9 out of 23 studies referred to the use of warfarin, heparin, urokinase, or other fibrinolytic drugs that could be associated with CES [5].

In patients with atrial fibrillation and documented atherosclerotic plaque during treatment with warfarin, CES was detected with an incidence of 0.7–1.0% per year [10]. There are cases of cholesterol embolization with inadequate use of anticoagulants (warfarin, Coumadin) [12] and with adequate anticoagulation [11, 13]. At the same time, there are studies showing that oral anticoagulant therapy has no effect on the risk of CES [14].

Currently, there is not enough data indicating a reliable causal relationship between anticoagulants, fibrinolytics and CES, and the available results are quite contradictory.

Diagnostic (catheterization of the left heart) or therapeutic interventions on the aorta and its large branches (coronary artery bypass grafting, carotid endarterectomy, mitral valve prosthetics, aortic-iliac and aortic-femoral bypass grafting) [5, 12, 15, 16] play a crucial role in the cause of CES. Therefore, most cholesterol embolizations are iatrogenic.

It was previously believed that femoral access for angiography is associated with a higher risk of CES than radial access. Later, no significant difference was found in the incidence of CES depending on vascular access. However, the risk of acute kidney injury (AKI), acute kidney disease (first 90 days after AKI) and chronic kidney disease as a manifestation of CES was significantly lower when using radial access compared to femoral access [17–19].

As the skills of personnel performing diagnostic and therapeutic interventions on the aorta and its branches improved, there a decrease in the risk of rupture of atherosclerotic plaque with the release of cholesterol emboli. At the same time, a higher incidence of CES is predicted due to the increasing number of diagnostic and therapeutic interventions on the heart and blood vessels [12].

There is also information on the possible development of CES in the case of damage to the atherosclerotic plaque fibrous cap with blunt abdominal trauma or falling [12].

Pathogenesis

Spontaneous plaque rupture due to anticoagulants and/or thrombolytics, or its direct trauma by a probe tip (catheter) during intravascular surgery results in the contents of the plaque core (cholesterol crystals (CC)) entering the bloodstream and the subsequent transportation to distal vessels (small arteries, arterioles and capillaries). Damage of plaques in the ascending aorta results in the embolization of the retina and brain; if plaques are located in descending and abdominal parts, the vessels of the gastrointestinal tract, kidneys, skin, and lower limbs are embolized [1–3].

Initially, CC embolization causes ischemic damage, and subsequent inflammatory reaction exacerbates the process. Activation of complement, renin — angiotensin — aldosterone system, oxidative stress, leukocyte aggregation and release of leukocyte enzymes lead to endothelial damage.

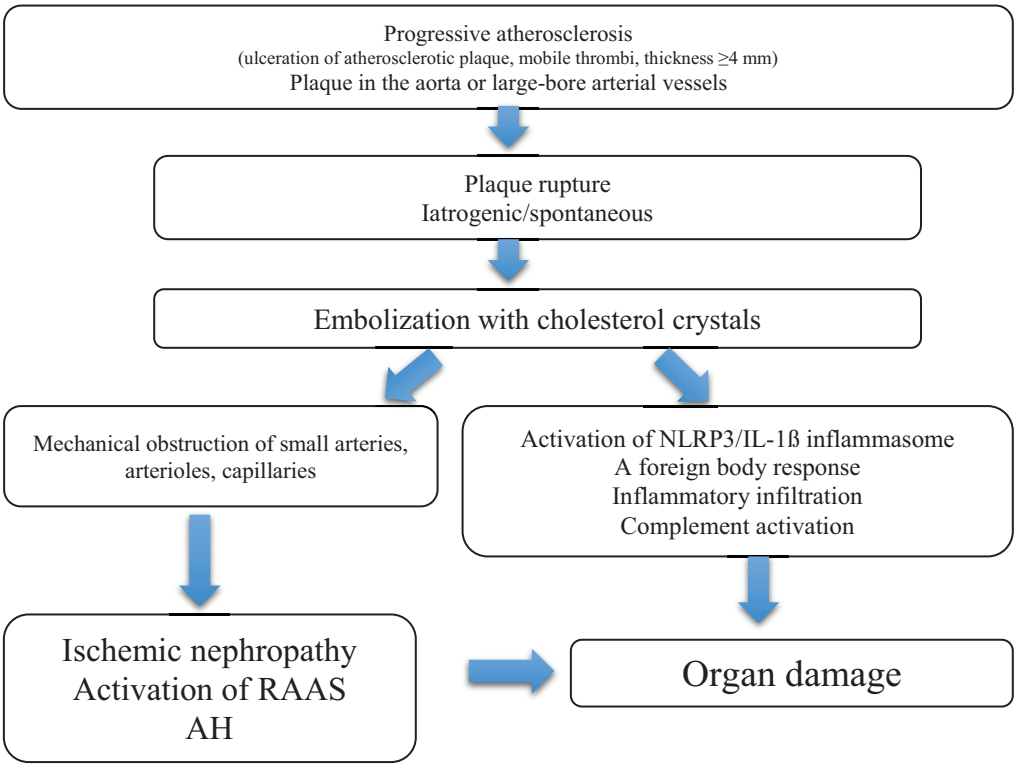

Figure 1. *Pathophysiological mechanisms of cholesterol embolization syndrome. (Adapted from A. Ozkok, 2019) [2]*

Note: AH — arterial hypertension; RAAS — renin-angiotensin-aldosterone system. IL-1ß — interleukin — 1ß

NLRP3 inflammasome is activated, resulting in the production of interleukin-1ß (IL-1ß) [20], and the secretion of other pro-inflammatory cytokines (tumor necrosis factor, macrophage inflammatory protein) is also induced [21]. Inflammation usually leads to intravascular thrombosis, followed by endothelial proliferation and fibrosis. The final result of CC embolization is the partial or complete occlusion of "target" arteries, which leads to tissue ischemia. Some episodes of microembolism may have no significant consequences, but massive embolism leads to systemic damage with the involvement of internal organs and the skin [1, 2]. Pathophysiological mechanisms of the development of CES are shown in Figure 1 [2].

Clinical Course

CES is characterized by a relatively long prodromal period between the triggering event and the onset of symptoms. Analysis of CES cases showed that skin findings were detected more than a month after the triggering event. However, if a fibrin thrombus can undergo recanalization (with partial restoration of vascular patency), cholesterol deposits do not undergo regression (cholesterol is insoluble in bodily fluids, and its crystals are not susceptible to phagocytosis by macrophages) [1, 2].

Clinical signs of CES vary. They reflect the systemic nature of the pathological process and are a combination of a systemic inflammatory response and symptoms that are typical for damage to the "end" organs. Inflammatory response often manifests in the form of fever, anorexia, weight loss, fatigue and myalgia, as well as several laboratory changes. The most common signs of CES are cutaneous and renal [14, 16, 22].

According to some authors, the skin and toes are affected in 75–96% of cases. Skin involvement is characterized by reticular asphyxia (livedo reticularis) in the form of a net-like reddish-blue pattern on lower limbs (lower leg, thigh) and sometimes on the body (lateral surfaces of the abdomen) [16, 23, 24]. Brown nodules that rise above the skin surface, i.e., palpable purpura, are a rarer skin lesion. The presence of palpable purpura indicates the development of leukocytoclastic vasculitis of small vessels as the body's response to the deposition of cholesterol microcrystals in said vessels. Along with a skin lesion, a symptom typical for CES may

appear — a cyanotic and cold big toe, with pulsation in the dorsal artery of the foot (the dorsalis pedis artery). Areas of soft tissue necrosis of the big toe may then appear and, in some cases, its gangrene, that requires amputation [11, 25, 26].

The incidence of kidney damage with CES is 92.2% [5, 26] and is defined as atheroembolic renal disease (ARD) that may be acute, subacute, or chronic [27, 28].

Massive embolization with CC may cause acute ARD during the first week after the trigger event. The course of AKI is progressive and is usually manifested by a sharp decrease in urine amount down to anuria; lower back pain resembling renal colic may arise. In period before anuria, urine color can resemble that typical for gross hematuria; blood clots may also be found in the urine. A sharp and difficult-to-manage rise in blood pressure (BP) is typical, sometimes accompanied by severe hypertensive encephalopathy and acute left ventricular failure [12].

ARD often has a subacute course with progressive renal dysfunction for several weeks [14, 16]. Chronic ARD is characterized by a slow and progressive decrease in renal filtration function. The chronic form is difficult to diagnose; it is often underestimated due to the absence of clinical (marked decrease in urine output) and extrarenal signs. Changes in urine sediment in the case of the chronic form are minimal: hematuria is rarely detected; cylindruria is usually absent [27].

The predominant lesion of renal tubulointerstitium may be accompanied by nocturia with a gradual decrease in urine specific gravity, which is confirmed by the results of the Zimnitsky test. Mild or moderate proteinuria is usually observed in cases of ARD. More rarely, in the case of induced focal segmental glomerulosclerosis, nephrotic proteinuria is detected [1, 5].

Lately, more and more publications on the development of CES after kidney transplant are emerging. CES of donor origin usually arises early after transplant and more often leads to allograft rejection. CES from the recipient's arteries becomes evident years after transplant, causing chronic allograft dysfunction, and is characterized by better organ survival. The prevalence of CES in this category of patients is expected to increase as the age of donors and recipients increases, and the donation criteria expand [29, 30].

Renal outcomes of ARD vary. Dialysis is necessary for 28–61% of patients (peritoneal dialysis may be advantageous since no anticoagulants are used), and 20–30% of patients have partially restored kidney function after several sessions [1, 5, 7, 11, 25]. Gastrointestinal symptoms (in 20–45% of patients) include abdominal pain, diarrhea, and bleeding. Cholesterol embolization of the visceral branches of the abdominal aorta may cause ischemia and fatal bowel infarction. Cases of necrotizing pancreatitis, focal necrosis of liver cells, and acalculous necrotizing cholecystitis were also described. In some cases, surgical interventions are necessary [31, 32].

Damage to the central nervous system can manifest as confusion, headache, dizziness, paraparesis, mononeuropathy. Cerebral artery embolization can occur with the development of transient ischemic attack, stroke, or spinal cord infarction. In such cases, CES usually results in diffuse brain damage with clinical signs of confusion and memory loss, rather than focal neurological signs and symptoms. Thromboembolism, in turn, is characterized by acute focal neurological symptoms [1, 33].

The pathognomonic symptom of CES is the presence of changes in the fundus in the form of specific Hollenhorst plaques (spots) that are associated with CC deposits. Embolization of retinal arteries (usually found in bifurcations of retinal vessels) leads to a sudden loss of visual fields (anopsia) with subsequent possible complete blindness. Hollenhorst plaques appear in the form of shiny and orange spots, with uneven contours, often with hemorrhage foci (Fig. 2). The most common source of these plaques is the carotid artery. This symptom is registered in almost 25% of patients. However, the presence of Hollenhorst plaques does not definitively confirm that the severity of the clinical picture is due to CES since these plaques can persist for more than a year and represent a previous attack of CES [34, 35, 36].

Myocardial and/or splenic infarctions, adrenal insufficiency, penile necrosis, tongue necrosis, and myositis were also described in cases of CES [37]. Damage to lungs during CES is rare [33].

Eosinophilia and/or hypocomplementemia can be registered simultaneously with skin lesions and general inflammatory reaction symptoms; they reflect the body's immune response to CC deposition in tissues. Blood eosinophilia is registered

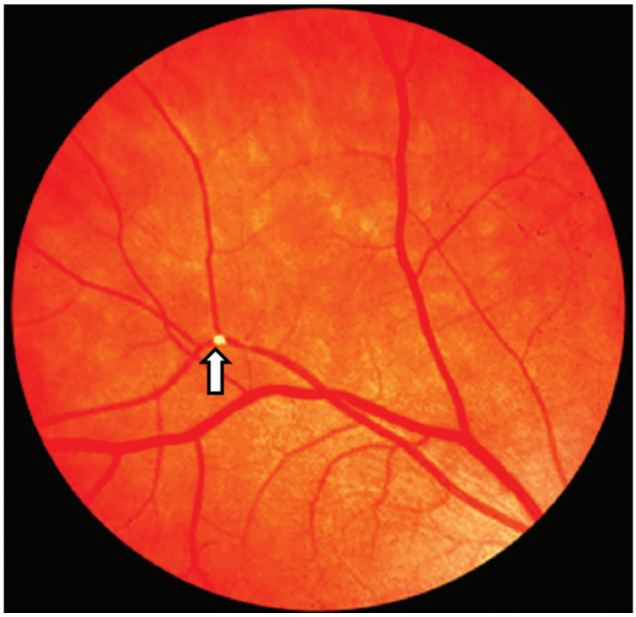

Figure 2. *Hollenhorst plaque when examining the fundus (Adapted from A.B. Dunlap, 2007) [36]*

in more than 60–80% of patients but is often observed only in the first few days [16, 22, 33]; the incidence of eosinophilia in tissues with underlying CES is unknown. The duration of eosinophil circulation in the blood is about 15 hours; in tissues (skin, gastrointestinal tract, connective tissues), it is 2–3 times longer, while eosinophils may return into the bloodstream. Eosinophils stop allergic reactions and inflammation (remove fibrin formed during inflammatory processes) and do not induce them. The severity of eosinophilia does not always correspond to the severity of the disease [38]. Less specific changes in laboratory parameters are: leukocytosis, anemia, thrombocytopenia, increased erythrocyte sedimentation rate, CRP, fibrinogen [22].

Diagnosis

The gold standard for CES diagnosis is tissue biopsy, which tissue can be obtained from the skin, muscles, kidneys, bone marrow, gastric mucosa and/or colon. Different stages of CES can be observed in the same biopsy specimen since CC-embolization can occur at different time intervals. Skin biopsy is a relatively non-invasive method, especially for taking material from the feet and legs; the method has a sensitivity of up to 92% [16].

The histological pathognomonic symptom of CES is the presence of biconvex and acicular CC or "cholesterol gaps" inside arterioles that appear due to CC dissolution during fixation of the biopsy sample [12, 16].

Kidney biopsy allows diagnosing CES in more than 75% of cases. Kidney biopsy helps to establish the diagnosis in more than 80% of cases of AKI but is very difficult in severely ill patients [26]. Since poor healing is observed at the sampling site, biopsy with underlying CES should be performed with caution. CES diagnosis can be established in practice in the presence of a combination of risk factors (triggering factors) and characteristic clinical symptoms. For example, clinical diagnosis of CES can be established after angiography, with delayed onset of AKI in combination with skin manifestations (livedo reticularis, lesion of the big toe). Tissue biopsy may not be required if CC are found in retinal vessels (Hollenhorst plaques) [1, 34, 35].

Differential Diagnosis

Since clinical signs of CES vary, with nonspecific features, the list of differential diagnoses is quite long, which allows considering CES one of the "great imitators":

- arterial thromboembolism;
- contrast-induced nephropathy;
- ischemic and/or drug-induced tubulointerstitial nephritis;
- endocarditis;
- aortic dissection (acute aortic syndrome);
- myxoma of left atrium;
- tuberculosis;
- pheochromocytoma;
- Raynaud's phenomenon;
- systemic diseases of connective tissue (rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis), vasculitis (polyarteritis nodosa), thromboangiitis obliterans;
- cryoglobulinemia;
- antiphospholipid syndrome;
- true polycythemia;
- thrombotic thrombocytopenic purpura and others [2]

First of all, CES should be differentiated from arterial thromboembolism, which usually causes acute ischemia and infarction of a "distal" organ. Although these two conditions have a common risk factor — progressive atherosclerosis, differential diagnosis is important since the prognosis and

treatment methods for these conditions are different. Thromboembolism usually starts suddenly and usually causes acute organ dysfunction due to ischemia and infarction. Clinical signs in cases of CES are usually subacute or chronic; dysfunction of the target organ is slow. Thromboembolism management should be started in a timely manner with anticoagulants, thrombolytics or interventional procedures. If optimal treatment is started earlier, then a good effect can be expected. CES management is more complex, the prognosis is usually worse, and anticoagulants, thrombolytics and invasive procedures can be more harmful than beneficial [1, 2].

During differential diagnosis, one should take into account the possibility of developing contrast-induced nephropathy (history of angiographic procedure), when AKI usually occurs within 48–72 hours after the procedure, and kidney function improves within 4–7 days. In contrast, renal dysfunction due to ARD usually has a subacute course with a gradual increase in serum creatinine within 1–2 months. Systemic manifestations of CES, including symptoms of damage to the skin, gastrointestinal tract, and central nervous system, may be useful in differential diagnosis [26].

Differential diagnosis with drug-induced acute tubulointerstitial nephritis can be difficult, especially in the presence of eosinophilia. The cause of eosinophilia in this case is considered to be allergic reactions (the so-called "glow of allergic fire") [38]. It should also be differentiated from acute and rapidly progressive nephritic syndromes.

Differential diagnosis of livedo reticularis varies greatly and includes a wide range of connective tissue diseases (Table.) [22, 33].

Prevention

CES is a manifestation of progressive atherosclerosis. Therefore secondary prevention of cardiovascular diseases is of primary importance in such patients. Secondary prevention measures are described in detail in the relevant domestic and foreign recommendations [39].

Patients with CES should avoid invasive interventional procedures whenever possible. An important preventive measure is a more rigorous and substantiated selection of patients for intravascular surgery. Radial access may be preferable in several aspects. Indirect angiography methods (contrast-enhanced magnetic resonance imaging, computed coronary angiography, etc.) should be used for diagnostic purposes in groups of patients at high risk. When performing the intravascular intervention procedure itself, much depends on the operator. The no-touch technique is recommended for manipulating guidewires and catheters through vessels, and also more thorough intraoperative removal of atheromatous contents using special devices. Although there is no proven relationship between anticoagulants, thrombolytics and CES, these drugs should not be used, only if they have no other indications (atrial fibrillation, valve replacement, etc.) [1, 2].

Treatment

There are no conventional protocols for the treatment of CES. Antiplatelet drugs are prescribed for secondary prophylaxis of cardiovascular diseases despite that there is no evidence for this as treatment of CES [15]. Statins can have three main positive effects for the treatment of CES: lowering the level of low-density lipoproteins; stabilizing atherosclerotic plaques; having pleiotropic anti-inflammatory effects (ability to directly reduce inflammation severity by blocking the expression of pro-inflammatory transcription factor (NF–B) and associated chemokines). Statins in patients with CES resulted in improved renal function and decreased skin manifestations [15, 40].

Inflammation is one of the main pathophysiological mechanisms in CES, and it was expected that anti-inflammatory drugs would be the main agents in pathogenetic therapy [40]. A clinical study including 51 patients with an established diagnosis of cholesterol embolism of intrarenal arteries assessed the effect of glucocorticosteroids (GCS) on short- and long-term renal outcomes. Patients of one subgroup (n = 32) received GCS with an initial dosage of 10–20 mg/day. The glomerular filtration rate was estimated at baseline, after 4 weeks and at the last follow-up stage (after a year). After 4 weeks, the glomerular filtration rate in patients taking GCS increased by 24% compared with the baseline, and in individuals not taking these drugs, it increased by only 5% (p = 0.03). However, this treatment had

no beneficial effect on the functional state of kidneys in the long-term [41]. Renal function significantly improved (serum creatinine level decreased from 7.5 to 1.6 mg/dl) with the administration of prednisolone per os and at a higher dose (1 mg/kg) [42]. Earlier, data were obtained on the decreased severity of renal failure and skin signs of cholesterol embolization due to the combination of GCS and cyclophosphamide [43]. Most studies suggest that GCS are preferable for CES [6, 42], although, in some cases, GCS had no proven efficacy and may have had a negative effect [7].

The ability of colchicine to block auto-inflammatory pathways (including NLRP3 and IL-1b) [44] and also reduce the risk of cardiovascular events was recently discovered [45]. There were reports of clinical cases of successful use of colchicine with corticosteroids in patients with CES and skin damage symptoms. [46].

The use of monoclonal antibodies of IL-1 antagonistsb (canakinumab) in atherosclerotic diseases [47] is a promising area with very promising results; it can certainly be considered for patients with CES. It was revealed that apheresis of low density lipoproteins reduced the need for dialysis for 6 months [48], and also improved symptoms in patients with CES [3].

Literature sources describe a case of improvement of skin lesion symptoms (blue toe syndrome) and prevention of toe amputation after lumbar sympathectomy [49].

Therapeutic measures for CES are limited, which is also associated with the lack of randomized controlled trials evaluating said methods of treating CES.

In general, the prognosis for CES is unfavorable, and mortality ranges from 15 to 30% during the first year of life [7].

Thus, CES is a multisystem condition and is often underestimated. Initially, CC embolization can have an asymptomatic course without visible signs, which significantly complicates the diagnosis. Also, due to a rather variable clinical picture, a practitioner of any specialty may encounter CES: cardiologist, nephrologist, dermatologist, gastroenterologist, neurologist, ophthalmologist, rheumatologist, surgeon. In clinical practice, physicians require constant clinical suspicion based on the knowledge of the risk factors, pathophysiological mechanisms and clinical picture of this pathology in order to establish the correct diagnosis and to determine optimal management tactics.

CES remains one of the least studied issues in cardionephrology. Therefore, further studies are necessary to determine optimal therapeutic strategies.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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Klimkin P.F. (ORCID ID: https://orcid.org/0000-0001-0002-0231-5909): collection and analysis of manuscript materials, writing and editing text

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