A renal disease frequently found at postmortem, but rarely diagnosed in vivo

A. Zuccala’ and P. Zucchelli
Malpighi Department of Nephrology, Policlinico S. Orsola-Malpighi, Bologna, Italy

Introduction

Cholesterol crystal embolism, also known as atheroembolic disease or cholesterol embolization, caused by showers of cholesterol crystals from atheromatous plaques lining the large arteries (usually the aorta), is a common postmortem finding in aged Caucasian patients with advanced atherosclerosis. Over the last decade it has become a growing cause of renal problems, but the diagnosis is frequently missed.

Case 1

A 65-year-old woman was referred to our Department for the presence of renal insufficiency of unknown origin. Her clinical history began in August 1985 when she was admitted to the Department of Internal Medicine of another hospital following a hypertensive crisis associated with a transient right-sided hemiparesis. For 7 years she had what was thought to be essential hypertension. Laboratory evaluation showed increased values of serum total cholesterol (242 mg/dl) and tryglycerides (289 mg/dl). Her serum creatinine was 2.0 mg/dl without urinalysis abnormalities. An intravenous pyelography was reported to be unremarkable and an abdominal ultrasonographic examination showed an abdominal aortic aneurysm measuring 2.8–3.3 cm. Funduscropy showed some arteriovenous nicking with no haemorrhages, exudates, or papilloedema. Complete recovery from hemiparesis was observed at discharge. She was subsequently treated with clonidine and diuretics.

In May 1996 she was admitted to an angiography unit for a swiftly resolved transient right hemiparesis. Her course was notable for the high urea nitrogen and serum creatinine levels. She was then transferred to our Department. The temperature was 36.8°C, heart rate 76 beats per minute, and blood pressure 140/90. On physical examination a carotid bruit (2/6) on both sides was evident, and livedo reticularis of the anterior thigh, lower abdomen and back was observed. Feet pulses were preserved.

Laboratory evaluation showed a slight proteinuria (1400 mg/day) and 3 white cells per high-power field in the sediment. No haematuria was present. Haematocrit was 28.3%, the white cell count 7300 mm3 and eosinophils 9.8% (720 mm3). Total cholesterol was 254 mg/dl, with a low HDL cholesterol of 36 mg/dl (normal range >40 mg/dl) and LDL cholesterol of 178 mg/dl. Lp(a) was 34 mg/dl (normal range <30 mg/dl), serum creatinine was 3.4 mg/dl with BUN of 40 mg/dl, ESR was 96 mm/h and C-reactive protein was 2.5 mg/dl (normal range <0.5 mg/dl).

Tests for antinuclear antibodies, antineutrophils cytoplasmic antibodies (ANCA) and serologic tests for syphilis were all negative. An abdominal ultrasonography examination showed smallish right and left kidneys (length 9.6 and 9.2 cm respectively) and confirmed the aneurysm of the abdominal aorta (diameters of 3.0–3.5 cm).

A percutaneous renal biopsy was performed.

Case 2

A 74-year-old man, a heavy smoker and with a long history of angina pectoris, was admitted to Cardiology Unit of our hospital in July 1996 for a cardiological evaluation. A coronarography via the femoral artery was performed and a critical stenosis of the left circumflex coronary artery was detected. A balloon angioplasty was successfully performed. Three weeks later, severe fatigue, worsening hypertension and an increase in BUN and serum creatinine occurred. In particular, serum creatinine, which was 1.7 mg/dl before the angioplasty, was found to be 3.7 mg/dl within 20 days of the manoeuvre. The patient was transferred to our Department.

Upon physical examination there were no remarkable signs apart from a haematoma at the right inguinal site. Livedo reticularis of the abdominal wall, buttocks and legs was evident. Temperature was 37.8°C, pulse 76 beats/minute and respiration 18. Blood pressure was kept in the normal range by metoprolol, amlodipine and doxazosine. The patient was also taking ticlopi-
Renal disease frequently found at post mortem but rarely diagnosed in vivo

1763
dine, simvastatin, and isosorbide nitrate. In the following days serum creatinine increased to 5.7 mg/dl and BUN to 70 mg/dl. The urinalysis documented a nephrotic-range proteinuria (3.7 g/24 h). The white cell count was 10 300 mm$^3$ and differential count showed 8.2% of eosinophils: Hb was 11 g/dl and the platelet count was 120 000. ESR was 110 mm/h, C3 was 65 mg/dl (normal range 90 mg/dl) and C4 was 12 (normal range >15 mg/dl). C-reactive protein was 8.9 mg/dl (normal value <0.5 mg/dl). Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibodies, cryoproteins, and antiphospholipid antibodies were negative. A percutaneous kidney biopsy was performed.

The two patients underwent percutaneous kidney biopsy even though the kidneys were reduced in size. Tissues for light-microscopy, immunofluorescence, and electron-microscopy were processed as previously reported [1].

Patient no. 1 had 5/12 hyalinized glomeruli. In the remaining glomeruli, an expansion of the mesangial areas together with a small increase in the number of cells were present. A mild thickening of the glomerular basement membrane was observed. There were no electron-dense deposits while a mild-to-moderate (2+) amount of C3 in the mesangium was seen. Clear cholesterol crystals were observed at electron-microscopy in three glomeruli (Figure 1). Arterioles showed a moderate intimal hyalination and thickened media. One arteriole had a lumen occluded by cholesterol clefts surrounded by mononuclear cells and eosinophil infiltrates (Figure 2). Tubular atrophy and moderate-to-severe interstitial fibrosis were also apparent. Patient no. 2 had 4/13 hyalinized glomeruli. The remaining showed ischaemic lesions or mesangial expansion with focal C3 deposits. A small necrotic area was present in one glomerulus, while in two glomeruli cholesterol crystals were present. Two arterioles and a small artery had the lumen occluded by cholesterol clefts (Figure 3), with moderate cellular infiltration around it. No foreign body giant cells were seen.

Comment

Peripheral embolization of small cholesterol crystals or cholesterol embedded within atheromatous emboli has been a well-recognized pathological entity even since Flory’s seminal description in 1945 [2]. Cholesterol microemboli (CM) are released from ulcerated or fractured atheromatous plaques involving the major arteries, particularly the aorta. CM is still considered a rare clinical event which mostly occurs in patients following invasive procedures. CM was, in fact, initially thought to have little clinical significance, frequently observed at autopsy, often representing incidental findings. In various autopsy series its frequency has varied enormously, i.e. 0.79–17%, as reported in Table 1 [3–11]. On clinical grounds, CM can manifest itself through a myriad of symptoms, easily causing confusion with other systemic diseases, or else it may be an indolent disease, slowly progressive renal insufficiency being the only sign.

Two major clinical forms may be present:

1. an acute or subacute scenario, usually following triggering mechanisms, and characterized by multiorgan involvement;

Fig. 1. Presence of cholesterol crystals in a glomerulus at electron-microscopy.
Fig. 2. Cholesterol cleft in an afferent arteriolar lumen surrounded by some infiltrating cells.

Fig. 3. Cholesterol emboli in a medium-sized arteriole.
Renal disease frequently found at post mortem but rarely diagnosed \textit{in vivo}.

Table 1. Reported incidence of cholesterol microembolization

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Study</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flory, 1945 [2]</td>
<td>Severe aortic atherosclerosis</td>
<td>Autopsy (n 267)</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>Moderate aortic atherosclerosis</td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>No atherosclerosis</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Kealy, 1978 [4]</td>
<td>Unselected</td>
<td>Autopsy (71 pts)</td>
<td>0.79</td>
</tr>
<tr>
<td>Ramirez \textit{et al.} 1978 [6]</td>
<td>Angiography</td>
<td>Autopsy (n 4578)</td>
<td>0.15</td>
</tr>
<tr>
<td>Jones and Jannacone, 1975 [10]</td>
<td>755 consecutive</td>
<td>Kidney biopsies</td>
<td>1.1</td>
</tr>
</tbody>
</table>

2. an indolent disease usually appearing spontaneously, with renal insufficiency progressing slowly over many months as the only sign, with absence of any specific diagnostic sign.

\textit{Acute or subacute manifestation.} CM typically appears following an invasive procedure such as angiography, cardiovascular surgery, percutaneous transluminal angiography of the coronary bed, renal arteries, or other arterial systems, and cardiopulmonary resuscitation. In addition it may appear during or after anticoagulant or thrombolytic therapy. Although the triad of lower extremity pain, livedo reticularis, and intact peripheral pulses has been claimed to be pathognomonic for CM, its presentation can be protean, with a variety of symptoms or signs masquerading as a systemic disease. Table 2 lists the main signs/symptoms [12–15]. Progressive renal failure is the main symptom which usually becomes manifest a few weeks after the procedure (3–8 weeks thereafter). This interval may be to blame for the many errors in diagnosis. At times progressive renal failure may be superimposed upon hypertensive nephrosclerosis in patients with longstanding hypertension. Non-oliguric renal failure may be associated with hypertension of recent onset or worsening of pre-existing hypertension. Moreover, after a plateau phase there may be a further rise in serum creatinine reaching the ESRD level after approximately 1 month. In a minority of patients, late recovery in renal function occurs, permitting discontinuation of renal replacement therapy after a few months.

Although a history of potential mechanisms may point to the diagnosis, the disease often goes undiagnosed because of the time lag and the presence of atypical symptoms. The diagnosis is straightforward when cutaneous manifestations are evident.

\textit{The indolent form.} This is usually characterized by the appearance of renal insufficiency in patients with longstanding hypertension. In patients with such indolent forms the diagnosis is likely to be missed unless a renal biopsy is performed, as is done in virtually all cases in Bologna. Even the biopsy results may remain inconclusive: it should be remembered that lipids are dissolved by the techniques used for the routine preparation of tissues for histological examination. In addition, as CM is a focal lesion it can elude the histological examination (both autopsy and biopsy).

Table 2. Non-renal manifestations of cholesterol embolization

| Skin            | Livedo reticularis, cyanosis (purple toe), gangrene, ulcerations, nodules, purpura |
| Nervous         | Transient ischaemic attacks, amaurosis fugax (bright and shiny yellow spots = Hollenhorst plaques in the retina), central paralysis, peripheral paraesthesia or paralysis |
| Abdominal       | Pain, nausea, gastrointestinal bleeding, bowel ischaemia, infarction or obstruction, pancreatitis, splenic infarct, adrenal insufficiency |
| General symptoms| Fever |

Table 3. Differential diagnosis in cholesterol microembolization

\textit{Acute or progressive form}

Endocarditis

Allergic interstitial nephritis

Malignant hypertension

Contrast-induced nephropathy

\textit{Chronic indolent form}

Hypertensive nephrosclerosis

Progressive oblitative renal artery atherosclerosis

Systemic vasculitis

\begin{tabular}{|l|l|l|}
\hline
Population & CM & Contrast nephropathy \\
\hline
Endocarditis & Ageds atherosclerotic & Diabetic, Myeloma \\
Allergic interstitial nephritis & 3–8 weeks & Few-hours–7 days \\
Malignant hypertension & & \\
Contrast-induced nephropathy & & \\
\hline
Recovery of renal function & Rare & Frequent \\
Hypertensive nephrosclerosis & & \\
Progressive oblitative renal artery atherosclerosis & & \\
Systemic vasculitis & Clinical associated findings & Purple toe, livedo reticularis etc. \\
\hline
\end{tabular}
unless the lesion is carefully sought in multiple sections. Some years ago we reported that approximately 25% of elderly patients with renal insufficiency and the clinical diagnosis of hypertensive nephrosclerosis had cholesterol crystals in the glomeruli or arterioles upon renal biopsy. No invasive procedures had been performed on them. In addition we carried out a prospective study on 56 consecutive patients admitted to our Department who were considered to have hypertensive nephrosclerosis; they constituted around 20% of patients with renal insufficiency accepted in 1993. When they were carefully studied, CM by renal biopsy was found in six of 19 patients with so-called atheromatous renovascular disease [16–18]. The diagnosis of spontaneous indolent CM with the clinical presentation of hypertensive nephrosclerosis is virtually impossible without a renal biopsy. The only clinical information pointing to the correct diagnosis is a history of a good control of blood pressure (particularly of diastolic blood pressure) in the years before the start of renal failure, and presence of severe and diffuse atherosclerosis with or without aortic aneurysm.

The typical patient is a male Caucasian, aged 60–80 years, a heavy smoker, with a history of coronary artery disease and other evidence of vascular disease, i.e. peripheral vascular disease, abdominal aortic aneurysm, carotid artery disease. More recently Mayo and Swartz [9] reviewed 402 consultation charts in a large academic institution, to define the incidence of CM among nephrological inpatients. They came to the conclusion that at least 4% of all inpatients examined and approximately 5–10% of all patients with acute renal failure had clinically significant atheroembolism. They stated that CM appeared at a rate of at least one case every 2 weeks. Moreover, these authors [9] and other investigators [19] admitted that the frequency of CM was probably underestimated in their series.

Various laboratory tests can help to establish the diagnosis of cholesterol embolization even though they are non-specific (Table 4). Nevertheless, the diagnosis can definitely be established only by renal biopsy (or biopsy of other affected organs). One must be aware of the fact that in paraffin-fixed sections cholesterol crystals are dissolved leaving needle-shaped clefts. On the other hand, in the frozen sections birefringent cholesterol crystals can easily be seen.

Because of the proximity to the main site of aortic atherosclerosis, and the high rate of renal blood flow, the kidneys are frequently involved. The pathogenesis of renal damage has not been completely resolved. Large zones of unaffected tissue alternate with wedge-shaped atrophic zones, giving rise to the suspicion that other mechanisms, apart from mechanical occlusion of the involved vessels, may play a role. Experimental studies [3,20,21] demonstrated intensive infiltration of eosinophils around the vessel wall immediately after microembolization, suggesting that eosinophils play a role in the pathogenesis of tissue damage. In vitro complement activation by atheromatous material causes polymorphonuclear leukocyte aggregation and release of toxic oxygen radicals [20,21]. The anaphylotoxic component C5a is chemotactic for eosinophils. This could explain the common eosinophilia in these patients. The participation of inflammatory reactions may be responsible for the often subacute (several weeks) or chronic (several months) course of the disease, but cyclical release of showers of cholesterol crystals cannot be excluded.

Therapy of CM is problematic. In patient with the full-blown picture of CM no therapeutic measure has resulted in proven benefit. In our experience, constant infusion of low-dose dopamine, pentoxifyllin, and ticlopidine, appear to be beneficial, but no controlled study has been performed. Discontinuation of anticoagulants and treatment of hypertension with a combination of calcium-channel blockers and ACE inhibitors are sensible. In the future, attempts to interfere with the inflammation accompanying cholesterol embolism may prove beneficial.

Prevention is important. All invasive manoeuvres and surgical procedures that are not strictly necessary should be avoided. The availability of new non-invasive diagnostic tools, such as spiral CT angiography, angio-MRT, and various types of colour-Doppler allow non-invasive evaluation of the majority of patients with vascular disease.

### Table 4. Laboratory tests of cholesterol microembolization

<table>
<thead>
<tr>
<th>Acute or progressive form</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated sedimentation rate</td>
<td>100</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>70</td>
</tr>
<tr>
<td>Elevation C-reactive protein</td>
<td>95</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>60</td>
</tr>
<tr>
<td>Serum complement decreased</td>
<td>25–30</td>
</tr>
<tr>
<td>Elevation serum transaminase or LDH, or amylase</td>
<td>50</td>
</tr>
<tr>
<td>Proteinuria (sometimes in the nephrotic range)</td>
<td>90</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>80</td>
</tr>
<tr>
<td>Eosinophiluria</td>
<td>?</td>
</tr>
<tr>
<td>Low platelets</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic indolent form</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small elevation C-reactive protein</td>
<td>?</td>
</tr>
<tr>
<td>Small eosinophilia</td>
<td>?</td>
</tr>
</tbody>
</table>

References

Renal disease frequently found at post mortem but rarely diagnosed in vivo.


