Cholesterol Embolization

From Pathological Curiosity to Clinical Entity

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SUMMARY
In the two cases of multiple system disease due to atheromatous embolization presented, increasingly severe hypertension developed owing to renal involvement. One patient had acute pancreatitis from embolization to the pancreas. The second patient had mottling of the skin of the legs. Purple toes were present and gangrene developed in 3 toes. The possible influence of anticoagulant therapy in promoting peripheral cholesterol embolism is discussed. It is suggested that the "purple toe syndrome" may be a manifestation of cholesterol embolization secondary to anticoagulant therapy.

Additional Indexing Words:
Anticoagulant therapy  Gangrene  Pancreatitis  Atheroma

For more than a century pathologists have observed cholesterol-rich emboli which seemed to be fragments of atheromata. Clinical manifestations have been associated with their presence, and such diverse conditions as acute pancreatitis, hypertension resulting from ischemic atrophy in the kidney, peripheral gangrene, and multiple system disease simulating polyarteritis are thought to have been caused, on rare occasions, by cholesterol embolization. But the diagnosis of cholesterol embolization has scarcely ever been made premortem.

Two cases of cholesterol embolization recently encountered at the Boston Veterans Administration Hospital are reported here. Our purpose is to publicize further the clinical aspects of the condition, and more important, to suggest that sometimes a causal relationship may exist between anticoagulant therapy and the cholesterol embolization.

Report of Cases

Case 1

R. L., a 54-year-old white man, had been hypertensive for 20 years and had been treated sporadically with sedatives and a low-salt diet. During a 6-month period prior to the final admission, he had lost weight and developed blurred vision. On admission October 1, 1965, he had blood pressure of 270/125 mm Hg, and during a hospital course of some 6 weeks, his diastolic pressure ranged between 100 and 150 mm Hg. The heart was enlarged, and there were no signs of congestive failure. The optic fundi showed arteriovenous nicking, yellow exudates, scattered hemorrhages, and blurred disk margins thought to indicate early papilledema. The clinical diagnosis was malignant hypertension. The initial hematocrit value was 28%, the blood urea nitrogen level (BUN) was 57 mg%, and the creatinine level was 4.8 mg%. Urinalysis revealed 2+ proteinuria, a specific gravity of 1.015, pH of 5.5, with 3 to 5 white blood cells and occasional granular casts in the sediment. He was given hydralazine (Apresoline), guanethidine, chlorothiazide, and potassium and had a stormy course with episodes of orthostatic hypotension, mental depression, and nausea and vomiting. On November 2, 1965, he complained of increasingly severe abdominal pain and his blood amylase was elevated to 1,110 Somogyi units. He was thought to have acute pancreatitis. Symptoms improved with nasogastric suction and intravenous feedings, but urinary output fell and BUN concentration rapidly rose to more than 200 mg%; with serum sodium level of 127, potassium 5.3, chloride 85, and carbon dioxide content 11 mEq/L. The electrocardiogram suggested hyperkalemia. The patient died in uremic coma on November 19, 1965.

Significant autopsy findings included an enlarged heart, weighing 550 g, with early fibrinous pericarditis and well-preserved coronary arteries...
and myocardium. The aorta, however, was so severely atherosclerotic as to be “shaggy,” particularly in the abdominal portion (fig. 1), with calcific and ulcerated areas to which soft, friable, brown-gray thrombotic material was adherent. Each kidney weighed 110 g, was dark red, had a thin capsule, an irregular “bumpy” external surface with depressed and elevated areas, and a narrow, pale, mottled cortex. The renal arteries were fully patent. The pancreas was enlarged and firm, showing on cut surface three ragged cavities from 1 to 3 cm across, containing pasty, greenish debris.

Striking microscopic findings were the numerous cholesterol emboli in the kidneys, pancreas, stomach, and spleen. Areas of ischemic atrophy of renal cortex were sometimes associated with these cholesterol emboli, which lay in arcuate and interlobular arteries. In addition, there was obvious hyperplasia of the walls of small renal arteries with fibrosis and intimal thickening, but with no evidence of necrotizing arteritis. The pancreas had many leukocytes, mostly neutrophils, in the interstitium and in duct and acinar lumina, with focal areas of necrosis and small abscesses, and, in addition, older areas of scarring and atrophy.

Case 2

A. W., a 47-year-old white man, was admitted to the Boston Veterans Administration Hospital on October 1, 1965, because of pain and discoloration of the toes. He had been well until March 1965 when myocardial infarction developed and hypertension and diabetes were noted. He was given anticoagulants and received warfarin sodium (Coumadin) for 5 months, into August 1965. During this time he noticed occasional mottling of the trunk and legs, with pain and soreness in the muscles of the lower part of the legs. The skin mottling stabilized and became constant in the month preceding his admission to the Veterans Hospital. His hypertension also became more marked, requiring antihypertensive drugs.

On admission, blood pressure was 200/100 mm Hg. The optic fundi showed arteriosclerotic narrowing of vessels and questionable blurring of disk margins. All toes were purple but not cold, the soles of the feet had purple mottling, and a faint mottling was also discernible on the calves and upper extremities, including the hands. Mottling of the legs was most prominent when they were hanging down. They blanched slightly when raised. Peripheral pulses were easily palpable in all extremities. The initial diagnoses were hypertensive arteriosclerotic cardiovascular disease, ecchymoses of the skin due to anticoagulant therapy, and possible vasculitis. Before studies could be carried out, the patient developed congestive failure with massive pleural effusion. He was given heparin because of a possible pulmonary embolus, but after a few days administration of heparin was stopped when melena and gastrointestinal bleeding requiring transfusion occurred. A total of 19 units of blood was administered, but the gastrointestinal bleeding was not controlled, and the patient died on the twenty-seventh hospital day.

The results of laboratory studies included initial hemoglobin value of 14.9 g%, white blood count 6,800 with normal differential count, bleeding time 2.5 minutes, clotting time 6 minutes, prothrombin activity 100%, platelet count 170,000 per cubic millimeter, VDRL (flocculation test) and LE preparations were negative, and the serum electrophoretic pattern was essentially normal. Values for serum BUN ranged from 15 to 25 mg%, and for cholesterol from 268 to 412 mg%. The concentration for fasting blood sugar was 152 mg%. Urinalysis repeatedly showed 2+ to 3+ proteinuria, specific gravity around 1.010, and essentially negative sediment.

At autopsy there was acute ischemic necrosis of three toes on the right foot, which were dark blue-black with focal desquamation of the skin. The heart was enlarged, weighing 525 g; the left ventricle was hypertrophied, and the aortic
valve showed minimal stenosis from old rheumatic valvulitis. Severe focal coronary atherosclerosis was noted, with an old recanalized occlusion of a large branch of the left anterior descending coronary artery. In the anteroseptal wall of the left ventricle was a wide subendocardial infarct, old and healed, but with an area of acute infarction at its edge. A second acute infarct was seen in the posterolateral wall of the left ventricle. The aorta was severely sclerotic, especially in its abdominal portion, with large ulcerated areas covered by greenish-gray, friable material. No narrowing of either renal artery had occurred, but a large atheromatous ulcer involved the medial half of the left renal artery ostium. The right kidney weighed 240 g, and the left kidney 180 g. Both kidneys had irregular external surfaces, with depressed red areas alternating with raised yellowish areas. These changes were particularly marked in the left kidney. The terminal gastrointestinal bleeding was from a perforated artery in the bed of a benign gastric ulcer.

Microscopic examination showed atherosclerotic ulcerative lesions of the aortic intima from which were protruding masses of pink-staining material containing abundant clefts; these were interpreted as the places from which cholesterol crystals had been dissolved in processing the tissue (fig. 2). Cholesterol emboli were present in the kidneys, pancreas, liver, and toes. In the kidneys these emboli had caused large areas of ischemic atrophy of tubules. Some arteriolar sclerosis was also present. In the pancreas, patchy areas of ischemic atrophy of acini were seen, and leading directly into a small pseudocyst was a fairly large (200 to 300 μ, internal diameter) artery occluded by a cholesterol embolus old enough to have undergone fibrous ingrowth. In the liver an old cholesterol embolus was associated with a small healed infarct. In sections from the toes, numerous cholesterol emboli, some old and fibrous, some organizing, some acute, were lying in small and medium-sized arteries deep in dermis and subcutis. The upper dermis did not

Figure 2
Atheromatous aortic ulcer at left renal artery ostium in case 2. Note characteristic slits for cholesterol crystals in a focally calcified amorphous mass. Slits reach shaggy luminal surface in upper portion, seen best in left upper quadrant. Original magnification, × 32.
have these lesions. Acute ischemic necrosis of the skin was noted.

Discussion

Pathological Features

Autopsy showed severe ulcerative atherosclerosis of the aorta in both our cases and cholesterol embolization was suspected in both cases during the gross examination because of the rather characteristic “bumpy” appearance of the kidneys (fig. 3). (This appearance may also be seen in polyarteritis nodosa, and the arteries occluded by the cholesterol emboli, the arcuate and interlobular arteries, are also the ones most characteristically involved by polyarteritis.) Most interesting is the fact that the cholesterol emboli do not usually cause classical renal infarcts, but instead areas of ischemic atrophy, often rather sharply defined. This has been considered due to incomplete occlusion, at least initially, for the earliest lesions microscopically show just the cholesterol cleft surrounded by nonagglutinated red blood cells, suggesting that blood continues to flow through the narrowed lumen. Later a more complete occlusion may occur due to a foreign-body giant-cell reaction and a fibrous ingrowth. Even this may occupy only part of the lumen in the manner of a mural thrombus, allowing recurrent embolization to the same vessel (fig. 4). These same phenomena of incomplete or recurrent embolization may explain the mottling of the toes, proceeding eventually to gangrene, as seen in case 2.

Hypertension and Renal Failure

Whether or not hypertension might be caused by cholesterol embolization has been discussed to some extent in the literature. Certainly the 20-year history of hypertension in our case 1 cannot be ascribed to cholesterol embolization, but the final accelerated phase of “malignant hypertension” is similar to that in the cases described by Handler, and whatever the initiating cause of the hypertension, it is clear that many of the renal arcuate and interlobular arteries were being occluded, over a period of at least several weeks to months, by these plugs of cholesterol-rich material and that areas of ischemic atrophy of the kidney resulted and led eventually, in case 1, to renal failure and increasing hypertension. In our case 2 renal failure did not develop but the kidneys were similar in many respects to those in case 1, and the patient had a history of hypertension with onset 7 months before death, during which time cholesterol embolization had been occurring.

Pancreatitits

Probstein and associates have presented evidence that cholesterol emboli may be a cause of pancreatitis, pointing out that the pancreas is, next to the kidney, the most frequent site of cholesterol embolization. It is important to note that in only one of the cases discussed by Probstein and associates was the clinical diagnosis pancreatitis, suggesting that cholesterol embolization must only rarely cause severe pancreatitis. In both of our cases there was evidence of damage

Figure 3

Left kidney in case 2. Note bumpy geographic appearance.
to the pancreas associated with cholesterol embolization. In case 1 this was severe enough to cause symptoms and a high serum amylase. We feel that careful histological study of the pancreas in both of our cases yielded evidence of a causal relationship between cholesterol emboli and areas of atrophy and inflammation.

**Peripheral Manifestations**

A “purple toe” syndrome has been described by Feder and Auerbach as a sequela of anticoagulant therapy. Clinically our second case seemed to be an example of this syndrome. Since here the blue mottling of the skin was clearly caused by peripheral cholesterol embolization, the question arose as to whether the “purple toe” syndrome was a peripheral manifestation of cholesterol embolization and indeed whether cholesterol embolization could be caused by anticoagulant therapy. The literature was reviewed to test the credibility of these hypotheses.

Of 121 cases of cholesterol embolization which we found in the English language literature, there were 16 in which peripheral manifestations were reported, that is, so-called livedo reticularis, gangrene of the toes, necrosis and ulceration of...
the skin of the lower extremities and muscle pain.\textsuperscript{12} Wherever (in 13 of these 16 cases) tissue from the affected peripheral area had been studied, cholesterol embolization of the arteries supplying that area was found. Furthermore, the therapy in six of the 13 cases was reported in sufficient detail to establish that anticoagulants had been administered prior to the manifestation of the mottling and other peripheral symptoms. A seventh case report,\textsuperscript{5} while omitting any mention of therapy, was otherwise detailed enough to suggest a likelihood that anticoagulants had been administered. The remaining six cases in which peripheral tissue had been studied were briefly listed in two large series,\textsuperscript{1, 10} and no information about therapy was presented. In only one of the three cases in which the affected peripheral tissue had not been studied, did the report contain information in respect to therapy and anticoagulants in these had been given.\textsuperscript{15}

Table 1 summarizes our case and the seven cases of cholesterol embolization in the literature in which both peripheral manifestations and therapy were reported. The case (Anderson's\textsuperscript{5}) in which anticoagulant therapy is probable is also included.

The onset of skin discoloration and other peripheral symptoms seems to occur no later

<table>
<thead>
<tr>
<th>Case</th>
<th>Anticoagulant given</th>
<th>Signs and symptoms in extremities</th>
<th>Time relationship to anticoagulant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geronimus and Merriam, case 2</td>
<td>+</td>
<td>Pain and soreness in leg muscles; pain in toes; blue toes; mottling of trunk and lower extremities; gangrene of toes</td>
<td>2-3 mo</td>
</tr>
<tr>
<td>Richards et al.,\textsuperscript{12} case 1</td>
<td>+</td>
<td>Livedo reticularis, purplish mottling, both legs to mid-thigh; tender nodules in left calf and thigh</td>
<td>Not clear; manifestations began in 4th week of hospitalization for myocardial infarct</td>
</tr>
<tr>
<td>Richards et al.,\textsuperscript{12} case 2</td>
<td>+</td>
<td>Painful, cold, tender legs; livedo reticularis, gangrene of toes</td>
<td>6 wk after onset of therapy</td>
</tr>
<tr>
<td>Anderson,\textsuperscript{5}</td>
<td>?</td>
<td>Intermittent claudication; blue toes</td>
<td>Not clear; manifestations began 11 wk after hospitalization for thrombophlebitis and myocardial infarct</td>
</tr>
<tr>
<td>Snyder and Shapiro,\textsuperscript{10}</td>
<td>+</td>
<td>Pain in toe; erythematous rash of feet, legs, and buttocks; gangrene of toe</td>
<td>3 wk</td>
</tr>
<tr>
<td>Sayre and Campbell,\textsuperscript{14}</td>
<td>+</td>
<td>Livedo reticularis of lower extremities</td>
<td>3 wk</td>
</tr>
<tr>
<td>Hoye et al.,\textsuperscript{8}</td>
<td>+</td>
<td>Patchy gangrene of both feet</td>
<td>2-3 mo</td>
</tr>
<tr>
<td>Fisher et al.,\textsuperscript{4}</td>
<td>+</td>
<td>Pain in buttocks and lower extremities; livedo reticularis, gangrene of toes</td>
<td>Not clear; given anticoagulants for pain</td>
</tr>
<tr>
<td>Uys and Watson,\textsuperscript{15} case 2</td>
<td>+</td>
<td>Incipient gangrene of toes.\textsuperscript{*}</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

\textsuperscript{*}No sections of toes taken, but cholesterol emboli present in other organs.

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than 3 months nor earlier than 3 weeks after the onset of anticoagulant therapy. In this connection it is interesting that in the only case of cholesterol embolization reported in which anticoagulants were given and peripheral symptoms not observed (case 1, Uys and Watson\textsuperscript{15}) the patient died within 3 weeks of inception of anticoagulant therapy. Generally the anticoagulant used was not specified. In one instance it was stated to be bishydroxycoumarin.\textsuperscript{8} In our case 2 it was warfarin sodium. When anticoagulant therapy was stopped in our case, these particular symptoms appeared to stabilize. Shortly before his demise, however, he received heparin therapy for several days because of a clinical suspicion of pulmonary embolism. At the time of death three toes were gangrenous. The evidence which we have just presented suggests that anticoagulant therapy may favor the peripheral dissemination of atheromatous fragments, possibly by preventing adequate thrombosis over ulcerated atheromatous lesions of the aorta. It appears therefore that anticoagulant therapy may well aggravate, if not actually initiate, cholesterol embolization. Because they may be concomitant with, or even precede, life-threatening systemic embolization, the peripheral manifestations of cholesterol embolization are a signal for the clinician to reappraise his treatment.

We have found little clinicopathological information in the literature bearing on our hypothesis. Feder and Auerbach\textsuperscript{19} lend support

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure5.jpg}
\caption{Junction of dermis with subcutaneous fat from skin of toes in case 2. An old cholesterol embolus, now organized, is seen. The embolus contains several slits from which cholesterol crystals have been dissolved. Original magnification, $\times 100$.}
\end{figure}
to it by noting that all six cases of their "purple toe" syndrome occurred 3 to 8 weeks after beginning anticoagulant therapy. However, they noted that the five biopsies taken were negative. The descriptions of these biopsies are brief and there are no pictures of the histological sections. These descriptions suggest however that these biopsies were taken too superficially to include arteries of a size large enough to have cholesterol embolization. The size of the involved arteries, according to several authors, ranges from 55 to 900 μ,6 66 to 530 μ,7 50 to 200 μ,8 or 54 to 715 with those most commonly involved measuring 150 to 200 μ,15 the limiting factor probably being the size of the individual cholesterol crystal or aggregate of crystals. In our case 2 the small arteries affected were deep in the dermis and subcutaneous fat (fig. 5). Even if adequately deep biopsies are taken, the lesion can be missed because it is not looked for specifically or because there are insufficient sections to demonstrate it.12

Addendum

Since this paper was submitted, a case report and review of the literature was published by Retan and Miller.20 The case reported was one presenting first with purple toes. This patient had been placed on dicoumarol for a myocardial infarct 6 to 7 weeks prior to onset of peripheral manifestations and thus supports our observation that these manifestations follow anticoagulant therapy.

References

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