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Clinical Pathologic Correlations

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Comparison of the Histopathology of Culprit Lesions in Chronic Stable Angina, Unstable Angina, and Myocardial Infarction

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Summary

Background: The etiology of unstable angina (UA) and myocardial infarction (MI) both involve rupture of an atherosclerotic plaque in a coronary artery. It has been suggested that the two syndromes differ because MI results if a red occlusive permanent thrombus occurs and UA occurs only if a nonocclusive platelet (white) thrombus occurs.

Hypothesis: The purpose of this study was to determine the differences between coronary lesion pathology in MI and UA and compare them with lesions of chronic stable angina (CSA).

Methods: We reviewed the pathologic specimens of culprit lesions obtained by directional coronary atherectomy in 27 patients with MI, 29 patients with UA, and 16 patients with CSA.

Results: The incidence of ruptured plaque was high and identical in patients with MI (77.8%), and UA (75.8%), and significantly lower in patients with CSA (25.0%) ($p < 0.001$). Similarly, the incidence of red thrombus was the same in MI (92.6%) and UA (82.7%), and significantly less in CSA ($p < 0.001$).

Conclusions: The underlying pathophysiology of both UA and MI appears to be the same, with red thrombus playing an important role in both syndromes. The only difference is in the degree of occlusiveness of the red thrombus on the ruptured plaque and whether the occlusion is transient (UA) or persistent (MI). The balance between thrombosis and endogenous clot lysis determines which syndrome occurs. Lytic therapy is not effective in UA, probably because the clot is not occlusive or because endogenous lysis has already achieved the degree of coronary opening that eventuates from tissue plasminogen activator or streptokinase administration. Prompt catheterization and revascularization may be as indicated in patients with MI if there remains viable myocardium as in patients with UA.

Key words: unstable angina, myocardial infarction, coronary pathophysiology, coronary thrombosis, plaque rupture, atherectomy

Introduction

The initiating event that results in an acute coronary syndrome, myocardial infarction (MI), or unstable angina (UA) has been felt to be the rupture of an atherosclerotic plaque in a coronary artery.[1–4] If this event is complicated by an occlusive red clot that remains in place long enough, the patient will have an acute MI. Recent data from angioscopy have suggested that if the ruptured plaque does not result in an occlusive red clot, but if there is only occurrence of a nonocclusive white clot made up primarily of platelets with some thrombin, UA will have occurred.[5,6] Over the past few years, with the advent of the Simpson atherectomy catheter,[7] it has been possible to obtain biopsies of coronary lesions in living patients. For better understanding of the pathophysiology of the acute coronary syndromes, we have reviewed our atherectomy findings in 72 patients with UA, recent acute MI, or chronic stable angina (CSA).

Methods

We reviewed the pathology of the tissue harvested from patients who underwent directional coronary atherectomy (DCA), using the Simpson athero cath device, at Saint Mi-

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FIG. 1 Histology of the atherectomy specimen from a 62-year-old man with a history of recent unstable angina who had directional coronary atherectomy of the left anterior descending culprit lesion. Note the intermixture of fibrous tissue, cholesterol clefts, calcium, inflammatory cells, and red thrombus typical of a ruptured plaque.

chael's Medical Center from November 1991 to December 1994. In all cases, the procedure was performed by one of four experienced interventionalists on a single lesion with stenosis >75% but <100% of the lumen diameter. In all, 72 patients who had undergone atherectomy were selected for retrospective review, as a comprehensive medical history was available indicating recent experience of an acute MI, UA, or CSA, and adequate biopsy specimens were available. An additional 31 patients had atherectomy during this time period, but because of inadequate clinical data or unavailability of pathology specimens they were not included in this study. Histology slides prepared by the pathology department were reviewed in a blinded fashion. The excised material collected in the housing of the athero cath was preserved in 10% formalin and processed by the histopathology department using H&E stain. Multiple slides of each specimen were examined by at least two of the authors under light microscopy and analyzed as to the presence of fibrous tissue, thrombus, ruptured plaque, calcification, cholesterol clefts, and inflammatory cells. Evidence of ruptured plaque was defined as the presence of thrombus, intraplaque hemorrhage, or fissure with or without calcification and cholesterol clefts within atheroma in a disorganized fashion (Figs. 1 and 2). These histologic findings are similar to those identified as ruptured plaque at postmortem examination[8] and correlated with the presence of complex coronary lesions at coronary angiography.[9] Statistical analysis was performed using the chi-square test.

Results (Table I)

Of the 72 patients studied, 29 (age 61.1 ± 12.0 years, 21 men) had UA, with the last episode of instability occurring within 14 days; 27 (65.4 ± 12.2 years, 19 men) had had MI within 14 days [including 15 who had received tissue plasminogen activator (TPA)]; and 16 (66.3 ± 11.2 years, 13 men) had CSA. The time from MI to atherectomy was 7.9 ± 2.9 days [mean ± standard deviation (SD)]. Two patients had had previous percutaneous transluminal coronary angioplasty (PTCA) of another lesion (both in the group with UA) and two had had prior DCA (one with stable angina and one

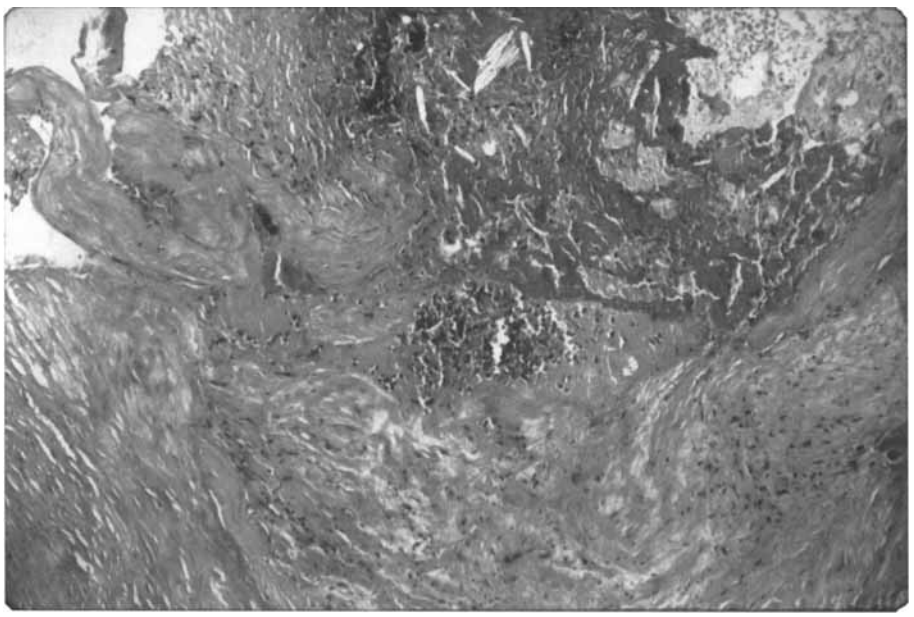

FIG. 2 Histology of the atherectomy specimen from a 71-year-old woman with a history of recent unstable angina who had directional coronary atherectomy of the right coronary artery culprit lesion. Note the intermixture of fibrous tissue, cholesterol clefts, calcium, inflammatory cells, and red thrombus typical of a ruptured plaque.

TABLE I Histopathology of specimens obtained from culprit lesions in chronic stable angina, unstable angina, and acute myocardial infarction

	UA (%)	AMI (%)	CSA (%)
Inflammatory cells	19 (65.5)	23 (85.2)	6 (37.5)[a]
Cholesterol clefts	26 (89.6)	25 (92.6)	12 (75.0)
Calcium	19 (65.5)	19 (70.3)	4(25.0)[a]
Fibrous tissue	28 (96.5)	23 (85.2)	14 (87.5)
Thrombus	24 (82.7)	25 (92.6)	5 (31.2)[b]
Ruptured plaque	22 (75.8)	21 (77.8)	4 (25.0)[b]

[a] $p<0.01$ CSA versus UA + AMI.
[b] $p<0.001$ CSA versus UA or AMI.
Abbreviations: AMI = acute myocardial infarction, CSA = chronic stable angina, UA = unstable angina.

with UA). Adequate specimens were obtained in all patients in the study, but three patients were considered to have had clinically unsuccessful procedures. Two patients underwent urgent coronary artery bypass graft (CABG), and one patient with a residual lesion >60% occlusion even after further balloon dilatation was maintained on medical therapy. Angiographically, type A lesions occurred in two patients with unstable angina pectoris, in one patient with MI, and in four with CSA; type B lesions occurred in 21 patients with UA, 21 patients with acute MI, and 11 with CSA; type C lesions occurred in 6 patients with UA, 5 patients with acute MI, and one patient with CSA ($p<0.05$ type A lesions CSA vs. UA + MI; no significant difference between UA and MI).

On histologic review of the atherectomy specimens, ruptured plaque was present in 75.8% of the patients with UA and 77.8% of the patients with MI compared with 25% of those with CSA ($p<0.001$). Similarly, thrombus was significantly more common in patients with UA (82.7%) and with recent MI (92.6%) than in those with CSA (31.2%) $p<0.001$. Inflammatory cells were found significantly more commonly in patients with acute coronary syndromes compared with those with CSA ($p<0.01$), especially in patients with MI. Calcification was present more commonly in patients with UA and MI ($p<0.01$), and there was a nonsignificant trend toward a higher incidence of cholesterol clefts in patients with acute syndromes. Fibrous tissue was present in most patients regardless of the clinical presentation.

In comparing the patients with UA with those with MI, there were no significant differences in any parameter. The incidence of thrombus and ruptured plaque was the same in the patients with MI and UA ($p>0.90$). Among those with MI, 15 of the 27 had received TPA. The histologic findings were the same in the patients with MI, with or without TPA.

Discussion

Although there is general agreement that atherosclerotic plaque rupture plays an etiologic role in the occurrence of both acute MI and UA, it remains unclear how the pathophysiology of the two syndromes differs. Utilizing coronary angioscopy in patients with unstable angina, Mizuno *et al.*[6] found only white clots associated with their ruptured plaques, that is, aggregated platelets and fibrin that are not occlusive, whereas patients with infarction were found to have occlusive red clots complicating their ruptured plaques. Therefore, they reasoned, in patients with UA, adhesion and aggregation of platelets occur in the area of plaque rupture, but the cascade leading to the formation of a large fibrin clot with associated red cells does not eventuate, whereas in patients with acute MI, the process goes on to completion with a resulting occlusive red fibrin clot. The waxing and waning of symptoms in patients with UA fits in with this observation since it is accepted that platelet aggregates commonly form and then break up, and are not necessarily persistently occlusive unless the fibrin cascade is initiated.

Our findings suggest that no such difference exists between UA and MI. The pathophysiology is essentially the same. Ruptured plaques occur in both syndromes, but regardless of whether the patient presents with UA or MI, the plaques are associated with red thrombus in addition to platelet aggregates. We found the same incidence of red thrombus in patients with unstable AP as in patients with MI. If the thrombus is totally occlusive and the occlusion persists for a sufficiently long period, MI will occur. If the thrombus is only partially occlusive, or if total occlusion is only transient and the vessel opens promptly, UA will have occurred.

The histologic findings indicating that the pathophysiology of both UA and MI are similar and differ only in the degree of occlusion or persistence of thrombus help to explain a number of previous observations and have some implications regarding management of both syndromes. First, evidence of ruptured plaques on arteriography and at postmortem examination is not uncommon in patients with a history of only CSA. Of the patients in this study with chronic AP, 25% had ruptured plaques histologically. Ruptured plaques probably occur often, but many result in only modest partial coronary occlusion and are asymptomatic. Probably only a few result in UA (more severe with intermittent total occlusion by clot) and only very few result in infarction (persistent total occlusion by clot). The cause of plaque vulnerability to rupture remains unclear but may be due to lipid composition of the plaque, plaque size, or the abundance or type of inflammatory cells in the plaque.[10] Mechanical factors, shear stress, hormonal changes, or unknown effects of aging may play a role.[11] Following plaque rupture, total occlusion is not inevitable, but a full spectrum of degree of occlusion with red clot is possible, as noted in this study.

Second, these findings of histologic identity between MI and UA help to explain the parallel beneficial effects of heparin and antiplatelet agents in UA and MI. The presence of red clot in both MI and UA suggests that red clot is probably repeatedly forming and lysing in both UA and MI and that there is a dynamic balance between clot formation and endogenous red clot lysis in both syndromes. If clot formation overwhelms the lytic ability, MI occurs; if lysis is repeatedly

successful and defeats occlusion by a clot, UA has occurred. In the management of both UA and MI, the patient does better if the balance is tilted away from clotting: patients with MI who are given aspirin have the same mortality benefit as if they were given streptokinase;[12] patients with UA who receive aspirin have many fewer infarctions or deaths than those who do not.[13] Patients with MI treated with massive doses of heparin have the same survival benefit as those given streptokinase;[14] patients kept on heparin who have UA have less frequent progression to MI or death.[15] In these instances, in both MI and UA, it appears that endogenous lysis of occlusive red clot occurs, and by inhibiting the coexisting clotting tendency, the severity of MI, or in patients with UA, the occurrence of MI is favorably affected. Recently, Hasche *et al.*,[16] showed that patients with MI had varying periods of "ischemic time" with ST elevation interposed with periods of no ischemia, suggesting opening and closing of total occlusions, that is, possible lysis of occlusive thrombus and then recurrent occlusive thrombosis. The extent of myocardial damage varied directly with the total time of ischemia.[16]

Third, these findings help to explain the disappointing effect of exogenous thrombolysis on mortality in patients with unstable angina.[17,18] In patients presenting with acute MI, the clotting process has overwhelmed the endogenous lytic capabilities and total occlusion has occurred. If the endogenous lytic capabilities are augmented by exogenous fibrinolytic agents such as TPA or streptokinase, the balance may go in favor of lysis and the totally occluded vessel will open and, if kept lytic (streptokinase) or if treated with heparin and aspirin, the vessel will stay open and a survival benefit and decrease in infarct size will result. In patients with UA, there is no total occlusion or there is only temporary occlusion. Endogenous lysis of the red thrombus has been successful (or the clot was never occlusive) and the patient is physiologically in the same condition as the patient who has had a successful lysis effect on a total occlusion by intravenous streptokinase or TPA. Administration of exogenous lytic agents to these patients will add little additional survival benefit,[17,18] but will cause them to suffer the same low but significant incidence of complications as do those with MI. As is the case in patients with MI after TPA, the patients with UA will benefit from heparin and aspirin to keep open the now open area that still has the presence of a ruptured plaque and superimposed nonocclusive red thrombus. Data on survival and recurrence of MI during 3-month follow-up in patients successfully treated with TPA or streptokinase are essentially the same as those in patients who have UA, that is, 2.5–3.5% of patients who undergo intravenous thrombolysis go on to an MI in about 3 months and 1.8% do not survive;[12] 2.7% of patients with UA go on to MI in 3 months and 1.5% do not survive.[19] This supports the identity of the pathophysiologic process in UA and MI.

Fourth, our findings explain the similarity in the arteriographic findings in patients with MI who have received TPA and those with UA. A similar degree of occlusion is found in patients after TPA as in patients with UA. Thus, in the TIMI II study of 1,461 patients after TPA who underwent routine catheterization, 12.1% had total occlusion of the culprit vessel, 75.3% had lesions of >60% occlusion, and 12.6% had no lesion of ≥60% occlusion.[20] Similarly, among 726 patients with UA (screened for inclusion in the Veterans Administration unstable angina study), 51 had normal coronaries and 38 had only lesions <75% (12.3%),[21] and of 75 patients with UA studied by Victor *et al.*,[22] 20% had normal coronaries or only lesions <70%, and 22 of 225 (10%) vessels studied were totally occluded. This similarity in coronary arteriographic findings supports the concept that patients with MI treated successfully with exogenous fibrinolysis show the same results as those with UA who have had sufficient endogenous fibrinolysis to open, or keep open, a clot superimposed on a ruptured plaque.

The logical clinical implication of this identity of the lesion pathology of MI and UA is that these patients should be managed similarly. It is usual to subject most patients with an episode of UA to coronary arteriography and then to revascularization if the angiographic anatomy is appropriate. Our findings suggest that MI should be managed similarly. If a stenotic or partially occluded culprit coronary artery is found, the patient should go to revascularization with angioplasty or coronary bypass as do patients with UA, especially if there is any preserved wall motion in the infarct area or if there is other evidence of viability of the area, for example, by rest radionuclide scanning.[23]

Conclusion

In summary, we have found that patients with myocardial infarction and patients with unstable angina have similar histologic findings on lesion biopsy obtained by transluminal coronary atherectomy. They have the same high incidence of ruptured plaque and of superimposed red thrombus, which is significantly higher than among patients with chronic stable angina. These findings of the identity of the pathophysiology of unstable angina and MI, except for the more persistent occlusion in MI, suggest a dynamic balance between clot formation and clot lysis in both unstable angina and MI, with endogenous lysis predominating in unstable angina and clotting predominating in MI, and support the use of antiplatelet and antithrombin agents in both syndromes. They also help to explain why thrombolysis is not effective in unstable angina whereas it is in MI. The similarity in pathophysiology suggests that management should be similar also, with invasive and revascularization strategies used more often in patients with MI, especially if the culprit lesion is not totally occluded.

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