Autopsy Findings of the Coronary Arteries of Variant Angina with Raynaud’s Phenomenon of the Tongue

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SUMMARY

A 42 year old man with variant angina occasionally associated with syncopal attacks died of acute myocardial infarction 17 months after the onset of angina. Prior to the onset of variant angina, he had Raynaud’s phenomenon of the tongue for 2 years. Both Valsalva maneuver and hyperventilation could repeatedly provoke chest pain and ST segment elevation in leads II, III and aVF. The infusion of prostaglandin E1 at a rate of 0.05 μg/kg/min, was able to prevent the attack of variant angina induced by these maneuvers.

Although coronary angiography performed 15 months prior to death revealed no organic lesions except for complete spastic occlusion at segment 1 following intravenous ergonovine, autopsy revealed marked intimal proliferation and accumulation of abundant glycosaminoglycans in three coronary vessels, as well as in small and muscular arteries of other organs.

This suggests that a rapid systemic progression of narrowing due to proliferation of the intima might occur in some cases of variant angina.

Additional Indexing Words:

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A recent report has described the high prevalence of migraine and Raynaud’s phenomenon in patients with variant angina, suggesting that...
diffuse arterial spasms may be the cause of these conditions.\textsuperscript{1)} However, histological examination of such cases, especially those of variant angina, is quite rare.\textsuperscript{2)}

We report here the autopsy findings of a case of variant angina with Raynaud's phenomenon of the tongue, whose histological findings showed marked intimal proliferation in three coronary arteries and also in the arteries of other organs.

**Case Report**

A 42 year old taxi driver suffered from Raynaud's phenomenon of the tongue for 2 years before his first admission. One month prior to his first admission, the subject suffered occasional chest pains during sleep and/or in the early morning. At 4 a.m. on June 15, 1981, he was awakened from sleep due to discomfort in the anterior chest of about 30 sec duration. Three min later he went to the toilet and lost consciousness immediately after urination. He regained consciousness a few minutes later, but continued to feel pain in the anterior chest. He was admitted into a hospital where he had anginal attacks at night and in the early morning 1 to 3 times per day. Nitroglycerin was effective for the relief of anginal pain. Two days later, he was referred to this hospital for further examination and treatment.

He smoked 2 packs of cigarettes per day and consumed 360 ml of alcohol (Japanese sake) daily. There was a history of syphilis. Family history was unremarkable.

On admission into this hospital, he appeared well. The pulse rate was 78 beats/min and regular, and the blood pressure was 132/86 mmHg. No lymphadenopathy was found, the thyroid gland was not enlarged and the

![Fig. 1](image_url) Fig. 1. The left panel is a normal electrocardiogram. The right panel is an electrocardiogram during anginal attack, which shows ST elevations in II, III and aVF.
lungs were clear. The heart was not enlarged; S₁ and S₂ were normal; no murmurs were audible. The liver and spleen were not palpable. No peripheral edema or cyanosis was noted. Neurologic examination was negative. The urine was normal. A stool specimen showed no occult blood. The hematocrit was 45.5%; the white-cell count was 4,800/mm³, with a normal differential count. The erythrocyte sedimentation rate was 4 mm/hour. The urea nitrogen was 21 mg/dl, uric acid 5.5 mg/dl, conjugated bilirubin 0.3 mg/dl, total bilirubin 0.8 mg/dl, cholesterol 123 mg/dl and protein 6.2 g/dl

Fig. 2. A: The upper panel is a trendgram of both heart rate and ST levels from a Holter ECG. The lower panels show the electrocardiogram at points (A) and (B). B: The Valsalva maneuver and hyperventilation induced ST elevation in aVF associated with angina. The ECG changes in aVF provoked by cold pressor test (top panel), Valsalva maneuver (middle panel) and hyperventilation (bottom panel). ST segment elevation associated with chest pain was provoked by both Valsalva maneuver (middle panel) and hyperventilation (bottom panel). Nitroglycerin was given at 6 min after hyperventilation.
Fig. 3. In the top panel, the Valsalva maneuver induced ST segment elevation in aVF. In the middle panel, the Valsalva maneuver did not induce ST segment elevation during PGE1 infusion. In the bottom panel, the Valsalva maneuver induced the same degree of ST segment elevation as before PGE1 infusion at 30 min after the cessation of PGE1 infusion.

(albumin 4.6 g/dl and globulin 1.6 g/dl). The sodium was 141 mEq/L, potassium 4.3 mEq/L and chloride 104 mEq/L. The glutamic oxaloacetic transaminase (GOT) was 12 IU/L, glutamic pyruvic transaminase (GPT) 104 IU/L, creatine phosphokinase (CPK) 76 IU/L, amylase 13 IU/L and alkaline phosphatase 5.4 K-A U/L. A test for C-reactive protein was negative and serologic tests for syphilis were positive. X-ray films of the chest revealed the heart and lungs to be normal. An electrocardiogram was normal with a normal sinus rhythm at a rate of 62 beats/min. However, the electrocardiogram taken during an anginal attack demonstrated ST segment elevations in lead II, III and aVF (Fig. 1). Cyclic ST segment elevation was demonstrated on Holter monitoring and second degree A-V block was evident during the elevation of the ST segment (Fig. 2-A).

Several provocative procedures such as the cold pressor test (immersing of the hand in water at 4°C, for 1 min), Valsalva maneuver (40 mmHg for 15 sec), hyperventilation (respiratory rate of 120/min for 2 min) were attempted. Although both Valsalva maneuver and hyperventilation repeatedly provoked the chest pain with ST segment elevations (Fig. 2-B), the cold pressor test did not cause these changes.

After the ST segment returned to the baseline level following the Val-
salva maneuver, PGE₁ was infused at rate of 0.05 μg/kg/min (Fig. 3). A few minutes later, the Valsalva maneuver was repeated in the same manner. However, neither ST segment elevations nor chest pain occurred during PGE₁ infusion. Chest pain and ST segment elevations were again induced by the Valsalva maneuver 30 min after the cessation of PGE₁ infusion. Prevention of ST segment elevation during PGE₁ infusion was demonstrated several times on different days. PGE₁ infusion prevented the ST segment elevations induced by hyperventilation as well. Atropine sulfate did not inhibit either Valsalva maneuver or hyperventilation induced ST segment elevation and chest pain.

The patient underwent right and left cardiac catheterization. All hemodynamics were normal. The left and right coronary arteries were normal on selective coronary angiograms. After intravenous administration of 0.2 mg of ergonovine maleate, the right coronary arteriogram demonstrated complete occlusion at segment 1 (Fig. 4). The electrocardiogram taken at the same time revealed ST segment elevation in lead aVF.

The patient had had Raynaud's phenomenon of the tongue 2 years before the anginal attack. His tongue became pale and hypesthesic on exposure to the cold air. The color of the tongue returned to normal as soon as he came back into a warm room. However, there was no time relation between the Raynaud's phenomenon of the tongue and the anginal attack. Ray-
naud's phenomenon of the tongue was not provoked by the Valsalva maneuver, hyperventilation, cold pressor or ergonovine, nor was it associated with ST segment changes or relieved by nitroglycerin.

The patient obtained relief from anginal attacks with 80 mg of nicardipine and 80 mg of isosorbide dinitrate, daily and discharged. However, 2 months later he had frequent attacks of chest pain and was readmitted. During the second admission, he was successfully treated with several drugs; 180 mg diltiazem, 4 mg molsidomine, 80 mg isosorbide dinitrate and 6 mg diazepam daily and was discharged. However, 3 months later, frequent anginal attacks recurred and the dose of diltiazem was increased to 210 mg, which effectively protected the patient from anginal attacks.

Seventeen months after the occurrence of the first anginal attack (26th November, 1983), he forgot to take his daily medication and suffered an acute myocardial infarction followed by a severe anginal attack and died.

**Autopsy Findings**

Autopsy permission was restricted to the chest and upper abdominal organs through a chest incision. The heart weighed 400 g. Both left and right coronary arteries exhibited severe intimal thickening with narrowing of their lumina (Fig. 5-A, D), which was observed diffusely from the origin to the distal portions. However, the arterioles were spared. The thick intima was composed of proliferated myointimal cells containing abundant glycosaminoglycans stained positively with alcian blue (Fig. 5-C), and increased collagen and elastic fibers (Fig. 5-B). Foamy cells were sometimes present. The inner layer of the media was focally infiltrated by lipid and glycosaminoglycans, with disarrangement of the smooth muscle cells. The smooth muscle cells were generally hypertrophic, but otherwise no significant changes were noted in the outer layer of the media and the adventitia.

The right coronary artery contained a fresh unorganized thrombus 3.7 cm from its origin in addition to severe intimal thickening (Fig. 5-D). There were scattered foci of degenerated myocardial fibers, consistent with fresh ischemic lesions, in the posterior wall of the left ventricle and in the posterior portion of the interventricular septum. Also noted were a few tiny fibrotic lesions with some mononuclear cells in the posterior wall of the left ventricle.

Similar diffuse intimal thickening was observed in the small arteries and muscular arteries of other organs, such as the stomach, intestine, kidney, liver, pancreas and periadrenal tissue. The lumina of these arteries as well as the coronary arteries were narrowed and formed a slit or starfish-like spaces in all portions. In the kidney, for example, a renal artery, interlobar and
Fig. 5. (A) Left coronary artery, showing severe diffuse intimal thickening and slit-like lumen. Elastica van Gieson stain, ×30. (B) Same section as (A). Azan stain, ×30. (C) Same section as (A). Alcian blue stain, ×30. (D) Right coronary artery, showing severe diffuse intimal thickening and a fresh thrombus in the lumen. Elastica van Gieson stain, ×30.

Arcuate arteries were involved, but the interlobular arteries and arterioles were spared of the lesion. Large elastic arteries, such as the aorta and subclavian arteries demonstrated similar intimal thickening. The intimal thickening of all the arteries mentioned above stained positively with alcian blue, suggesting an abundant accumulation of glycosaminoglycan. There were no such histological features as vertical arrangement of endothelial cell nuclei, localized edema in the subendothelium or media, and disarrangement of internal elastic lamina, elastic fibers and smooth muscle cells in the arterial walls, which are said to be observed in the case of vasospasm. The arteries and veins of the lungs exhibited no histo-pathological changes. There were no features of angiitis in the 45 sections examined from various organs.

**DISCUSSION**

This case had presented with variant angina with normal coronary arteries on angiography. Fifteen months later, however, the autopsy revealed marked diffuse narrowing of three coronary arteries mainly due to proliferation of the intima. Although it is well recognized that selective angiography
during life tends to underestimate the actual degree of luminal narrowing, the discrepancies observed in the present case are striking.

It has been demonstrated by Gensini et al\(^3\) and Kramer et al\(^4\) that the localized atherosclerosis of coronary arteries may progress rapidly in some cases. Maseri et al\(^5\) proposed that spasm may play a role in localization and development of atherosclerotic plaques, probably due to the stimulated intimal smooth muscle proliferation with platelet aggregation.\(^8\) However, the autopsy findings of the present case are quite different from these reports.

Histological findings from the coronary arteries were similar to those of diffuse coronary sclerosis,\(^9\) characterized by fibrous proliferations within both media and intima following an associated excess in glycosaminoglycans. However, a diagnosis of diffuse coronary sclerosis would not be compatible with our case, because the changes in diffuse coronary sclerosis occur in infancy and/or childhood. Although proliferative endarteritis had to be ruled out, there were no features of angitis in 45 sections examined from various organs.

Although the intimal thickening of arteries had already progressed to some degree at the time of coronary arteriography, it should be judged as a rapidly progressive systemic arteriosclerosis for the reasons mentioned above. Recently, El-Maraghi et al\(^10\) demonstrated an autopsy case of acute myocardial infarction due to coronary arterial spasm. The present case lost his life due to an acute myocardial infarction following a prolonged arterial spasm resulting in thrombus formation in the coronary artery\(^11\) (Fig. 5-D).

Though there is reasonable explanation for the relation between the spasm and the intimal thickening with abundant accumulation of glycosaminoglycans, a marked increase of intimal thickening such as seen in our case could easily narrow the arterial lumen by slightly changing the arterial tone.

This case had Raynaud’s phenomenon of the tongue 2 years prior to the onset of anginal attacks. Raynaud’s phenomenon of the tongue is a rare disorder. It has been reported in patients with scleroderm\(^12\) and patients with Raynaud’s phenomenon of the hand.\(^13\) Our case, however, had no evidence of scleroderma, nor Raynaud’s phenomenon in other parts of the body.

Recently, Miller et al\(^11\) reported the high prevalence of migraine and Raynaud’s phenomenon of the hand in patients with variant angina, concluding that migraines and Raynaud’s phenomenon commence some years before the onset of variant angina. Raynaud’s phenomenon of the tongue in this case appeared 2 years prior to the onset of variant angina. However, the episodes of angina were not related to attacks of Raynaud’s phenomenon and nitroglycerin or calcium antagonists were not effective in the relief of
the attacks of Raynaud's phenomenon of the tongue. Unfortunately, the arteries of the tongue were not examined. ST segment elevations and anginal pain were reproduced by both Valsalva maneuver and hyperventilation. Prostaglandin E₁ infusions were effective in preventing both the ST segment elevations and anginal pain induced by these procedures. Chierchia et al used prostaglandin I₂ infusions in 9 patients with variant angina, but found that they were effective in reducing the number of ischemic episodes in only 1 patient who had liver dysfunction. Our patient also had liver dysfunction. We, however, could not determine whether or not the effect of prostaglandin E₁ on the coronary spasm induced by Valsalva maneuver and hyperventilation was related to liver dysfunction.

In this report, we have described the autopsy findings of the coronary arteries of a patient with an unusual variant angina with Raynaud's phenomenon of the tongue. Also, we have shown that coronary spasm induced by both Valsalva maneuver and hyperventilation in this case was inhibited by the infusion of prostaglandin E₁.

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REFERENCES

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