

Clinicopathologic Session

Case 2/99: a 40-year-old woman with a pericardial effusion

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A forty-year-old woman was admitted to the hospital for the treatment of a pericardial effusion. The patient was originally from Picos, state of Piauí in the northeast of Brazil, but was currently living in São Paulo. She had a history of four previous pregnancies (including one miscarriage). Seven months prior to admission (October, 96) she had respiratory-dependent chest pain and, after seeking medical attention, bacterial pneumonia was diagnosed. Two months thereafter (December, 96) she had headache, vomiting and fever. At that time, as part of the diagnostic evaluation, she underwent a computed tomographic scan of the brain and SNC fluid examination. She was given the diagnosis of viral meningitis.

After three months (March, 97), she complained of right groin pain. She sought medical attention and a right femoral artery aneurysm was diagnosed. Surgery was recommended. During surgery, what was actually observed was a pseudoaneurysm of the femoral artery. Two weeks later, she needed reoperation due to local bleeding at the arterial suture site.

In May, 1997 (two months after surgery), she had right internal jugular vein thrombosis and started complaining of episodes of chest pain radiating to the neck and left shoulder. The episodes occurred at rest, had a duration of 3 minutes and were relieved by nitroglycerin.

The diagnostic evaluation at the time (May, 97) included cardiac catheterization, coronary angiography and left ventriculogram. Hemodynamic data are presented in table I.

The coronary angiographic examination showed three right coronary artery aneurysms and a distal 90% stenosis. Left main and left anterior descending coronary arteries were free of significant lesions. The circumflex artery was occluded after the emergence of the marginal branches. Left ventriculogram showed akinesis of the basal portion of the posterior wall and of the inferior wall, suggestive of left ventricular pseudoaneurysm of the posterior wall.

At that time, the patient developed painful oral lesions that prevented her from eating. Three days later chest pain recurred; it was more intense in the dorsal decubitus position and less intense when she was seated. On physical examination, a pericardial friction rub was noted. Chest

radiogram disclosed an enlarged cardiac silhouette, suggestive of pericardial effusion. The patient was then referred to the Heart Institute for treatment.

On physical examination (May, 97), the patient was severely ill. Her blood pressure was 90/50mmHg and her heart rate was 100 beats per minute. The lungs were clear. Cardiac examination showed normal heart sounds, no murmurs and a pericardial friction rub. Abdominal examination was normal. Her right leg had a lower temperature and no arterial pulse.

Laboratory results showed hemoglobin 8.3g/dL, hematocrit 24%, 3,100,000 red cells/mm³, mean corpuscular volume 77μ³, mean corpuscular hemoglobin 27pg, 12,800 white cells/mm³ (3% rods, 68% neutrophils, 0% eosinophils, 17% lymphocytes, 12% monocytes), 376,000 platelets/mm³, erythrocyte sedimentation rate of 65mm in the first hour. Serum glucose was 97mg/dL, urea was 19mg/dL, creatinine was 0.6mg/dL, sodium was 137mEq/L and potassium was 4.5mEq/L. Prothrombin time was 17.1 seconds (control value 11.4), INR was 2.34 and partial-thromboplastin time was 34s. Protein electrophoresis disclosed total protein 6.9g/dL, albumin 3.4g/dL, α₁-globulin 0.2g/dL, α₂-globulin 0.5g/dL, β-globulin 0.7 g/dL and β-globulin 2.1 g/dL.

An electrocardiogram showed sinus rhythm at a rate of 115 and QRS axis at – 30° toward the back. There was an inferior wall infarction, a probable dorsal infarction and diminished electrical forces of the lateral wall (fig.1).

A cardiac ultrasonographic study showed an image suggestive of a pseudoaneurysm in the left ventricular inferior wall. Its opening orifice measured 12mm. There was a moderate-sized pericardial effusion and mitral regurgitation. There were no pathological changes of the leaflets and chords. Left ventricular dysfunction was considered moderate and there were no signs of cardiac tamponade.

On the morning of her 3rd hospital day, she developed sudden onset cardiogenic shock, cardiac arrest and electromechanical dissociation, followed by death.

Discussion

Echocardiogram - Left ventricular pseudoaneurysms can be caused by myocardial infarction, trauma, infectious endocarditis or after cardiac surgery, especially surgery involving mitral valve repair or ventriculotomy. The presence of a pseudoaneurysm is associated with high morbidity, related to arrhythmia, heart failure and systemic emboli. The untreated pseudoaneurysm usually results in cardiac rupture and sudden death. Its early diagnosis is,

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Table I – Cardiac catheterization (pressures in mmHg)				
Chamber	Systolic	Early diastolic	End diastolic	Average
Left ventricle	105	0	14	
Aorta	105	65		78

thus, very important, considering that surgical correction is generally successful¹⁻³.

Among the noninvasive tests, ECG and chest radiograph have low sensitivity and specificity resulting in the need to use more sophisticated tests, such as the echocardiogram, the computed tomographic scan or radionuclide angiography¹⁻⁵.

The echocardiogram, especially two-dimensional, color and Doppler analyses, yields a fast and precise diagnosis of this condition. Diagnostic signs include: the presence of a paracardiac sacular cavity with systolic bulging and echo free interior, and the presence of a myocardial discontinuity with a narrow neck linking the ventricle and the cavity. The flow analysis shows flow toward the pseudoaneurysm during systole and reverse flow during diastole. Differential diagnoses include pericardial cysts, hematomas, localized pericardial effusions and diverticula. In none of these conditions is there blood flow from the ventricle, characterizing the presence of a pseudoaneurysm^{2,4-5}.

In the present case, the echocardiogram showed a left ventricular pseudoaneurysm of the basal portion of the posterior wall, with a neck of 13mm and systolic flow to the pseudoaneurysm, systolic bulging and the presence of a moderate-sized pericardial effusion, indicating the severe clinical condition and the need of surgery.

(Dr. Marcelo Luiz Campos Vieira)

Clinical aspects - Since the main aspect of the disease is the arterial involvement, especially of small-sized arteries, in the presence of inflammatory markers, the diagnosis must involve a vasculitis syndrome. It is a clinicopathological disorder characterized by inflammation and necrosis of blood vessels, causing ischemia of the tissues downstream. One important aspect to consider about vasculites is their great heterogeneity and the overlap among the syndromes, which creates difficulties in diagnosis⁶.

Giant cell arteritis affects especially women over the age of 55. Its etiology is unknown and pathological aspects include the panarteritis with mononuclear cell infiltrate and the frequent formation of giant cells. The classic presentation of the disease is a triad composed of severe headache, fever and malaise, usually associated with other symptoms. Erythrocyte sedimentation rate is high and there is hypochromic anemia. As the initial manifestation of the disease, this syndrome can involve the aorta and its branches, including, rarely, the coronary arteries. Venous involvement is unusual. Therefore, the aspects of the present case are not typical of this vasculitis.

Churg-Strauss disease is rare. Its onset can occur at any age (44 years old on average). It is characterized by a multiple organ vasculitis, which can involve the venous system and the coronary arteries. The disease targets preferentially the lungs, causing severe asthma and increased eosinophilia, which were not seen in the present case. Seventy percent of the patients have skin involvement.

The heart can also be involved in Wegener granulomatosis. Although rare, cardiac involvement has occurred in up to 12% of the cases in some series. The disease is characterized by the presence of necrotizing granulomas in the respiratory tract (95% of the cases) and in the kidney (85% of the cases). Their absence precludes the diagnosis.

Rheumatoid arthritis can also result in coronary involvement; however, the clinical presentation is mainly related to a disease affecting multiple joints. At autopsy, coronary lesions are seen in 20% of the cases, rarely causing myocardial necrosis⁷.

Another vasculitis-associated disease, eventually implicated in coronary artery involvement, is systemic lupus erythematosus (SLE). Its etiology is unknown and pathogenesis is related to the destruction of tissue by autoimmune antibody and antigen-antibody complex deposition. Ninety percent of the cases are women, usually of child-bearing age. Diagnosis is achieved by the presence of laboratory tests, indicating the presence of autoantibody and at least two clinical manifestations of the disease. In the present case we, unfortunately, do not have autoimmune laboratory data, but the patient had several clinical characteristics of the disease, such as oral ulcers, venous thrombosis, aseptic meningitis and miscarriage which make lupus one of the most likely diagnoses for this case.

Ischemic heart disease was observed in 16% of the patients in a series of 100 prospectively assessed patients with SLE. This involvement followed two different patterns: Cardiac disease occurred early following the other manifestations of the vasculitis or was associated with the prolonged use of steroids. In the latter patients, coronary disease was predominantly atherosclerosis and was deemed to be the atherogenic effect of the prolonged use of steroids.

Kawasaki disease can result in vasculitis and myocardial infarction. It usually occurs in children; however, it

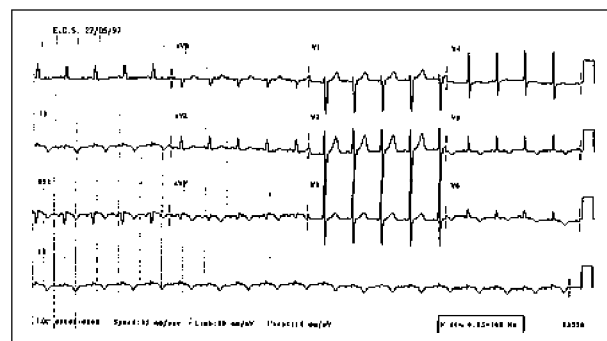


Fig. 1 - Electrocardiogram - tachycardia, sinus rhythm, Left anterior hemiblock and inferior, dorsal and lateral myocardial infarction.

can occasionally involve adults. Its main consequence is precisely the development of coronary artery aneurysm, affecting 17 to 31% of the cases, with a mortality rate of 1 to 3%. The clinical aspects of the disease include bilateral conjunctivitis, fever, mucous changes, edema, desquamation, rash and the presence of enlarged lymph nodes (diameter >1.5cm). It is also a disease of an acute course, not long-lasting. The present patient did not have these characteristics.

Polyarteritis nodosa is a systemic necrotizing vasculitis involving small- and medium-sized arteries, frequently affecting renal and visceral arteries. It has also been implicated as a cause of myocardial infarction. The mean age of onset is 45 years and it is twice as frequent in men. Thirty percent of the patients have hepatitis B antigens⁸⁻¹¹.

The vascular lesions are segmental and preferably involving bifurcation and branching sites. Rarely, neighboring veins are affected. During the acute phase of the disease, there is a neutrophilic infiltrate throughout the vessel as well as in the perivascular area, resulting in intimal proliferation and degenerative changes of the vessel wall. Arterial dilations of up to 1cm are common in the classical syndrome.

In one study, half of the 36 patients studied had coronary involvement. Only in 4 of these were there large areas of myocardial fibrosis and in six just small scars¹². Only one patient had a clinical myocardial infarction. Despite the high prevalence of coronary disease, angina is seldom reported.

Laboratory results are not specific. In 75% of the cases there is increased white cell count, especially neutrophils. Chronic disease anemia, high erythrocyte sedimentation rate and hypergammaglobulinemia are often detected.

The association of arterial, venous, cardiac involvement and arterial dilations as well as its frequency among the vasculitis make polyarteritis nodosa one of the most likely diagnoses in this case. Survival without treatment is 13% in five years. In patients treated solely with steroids, survival increases to 50%, reaching 80-90% in patients treated with the association of steroids and immunosuppressive agents^{13,14}.

Behçet syndrome is now considered an autoimmune disease, associated with the presence of HLA B-51. The diagnosis is largely clinical, with recurrent oral ulcers, genital ulcers, skin or large vessel vasculitis, arthritis and meningitis. The prevalence in Europe, the USA and Japan is approximately 1:500,000 people. It affects mostly young men.

The oral ulcers are painful, measuring 1 to 2mm, with a yellowish base. Vaginal ulcers can be pain free. Systemic symptoms occur in 63% of the patients. Uveitis can be severe and, in Japan, is responsible for approximately 15% of the cases of acquired blindness. Venous thrombosis is seen in 25% of the patients. In 500 patients followed for 12 years, 10 cases of arterial lesions occurred¹⁵. Nine of these patients were men, and none had coronary involvement. A study of 1200 patients followed for eight years showed a 1.6% arterial involvement, the femoral artery being the most affected vessel. Again, no coronary events were reported¹⁶.

In another study composed of 15 Behçet patients,

heart disease was reported in six, mostly mitral valve prolapse¹⁷. Silent ischemia was present on Holter monitoring in 9 of 36 patients with Behçet disease whereas it was present in only one of 38 controls ($p < 0.001$)¹⁸. Seven of those patients had normal coronary angiograms.

The most common laboratory changes are increased white cell count and erythrocyte sedimentation rate. Pathological aspects are not specific at microscopy. The treatment includes steroids in severe cases. In patients with uveitis the most prescribed drugs are colchicine and cyclosporine. Chloranbucil and azathioprine have also been used with variable results.

It is worth remembering that cardiac tumors, especially mixomas, can cause systemic symptoms and many different laboratory changes, including hypergammaglobulinemia, and increased erythrocyte sedimentation rate, possibly caused by the secretion of inflammatory mediators, such as interleukin 6 or tumor necrosis factor. Since, in these cases, the cardiac findings are not specific and can be absent, it is not rare that these patients are diagnosed with autoimmune disease, infection or paraneoplastic syndrome.

Tumor fragments and thrombi embolization can result in infarcts and visceral hemorrhage, including the heart and the formation of vascular aneurysms that can mimic vasculitis. Although this is more frequent in cases of mixomas, it can happen with any cardiac tumor.

Even if, in the present case, the echocardiogram did not show an image of a tumor, its best sensitivity is for luminal mobile tumors, with much less sensitivity to detect intramyocardial and nonmobile ones. The latter are, however, unlikely but cannot be completely ruled out in our case.

Among the hypotheses discussed, the most likely are SLE, polyarteritis nodosa and Behçet syndrome. Perhaps the latter one is the most probable due to the greater number of diagnostic criteria present in our case: oral ulcers, large vessel vasculitis, aseptic meningitis, and because it is a convenient explanation for the association of venous thrombosis, arterial aneurysms (and pseudoaneurysms) and the oral ulcers. The low prevalence and rare involvement of the coronary arteries in this disease, however, brings this hypothesis into question. I emphasize also that the two other hypothetical diagnoses are more prevalent in the population and especially polyarteritis nodosa may result in this association.

The observed pericarditis could be caused by a myocardial infarction. Approximately 25% of the patients with Q-wave myocardial infarctions develop pericarditis 12hs to 10 days after the event. Seventy percent of the patients with a pericardial friction rub have respiratory-dependent or positional chest pain.

Both the echocardiogram and the ventriculogram disclosed the presence of an inferior wall pseudoaneurysm. Since this complication is recognized as having a very high mortality rate, the cause of death most likely was cardiac rupture, which occurs in up to 10% of the deaths after a myocardial infarction.

(Dr. Mauricio Bernstein)

Clinical diagnosis - Behçet Syndrome, polyarteritis nodosa or SLE.

Necropsy

The heart weighed 450g. After opening the pericardium, 200mL of unclotted blood were obtained. At the posterior wall of the left ventricle there was a saccular structure, similar to an appendix, measuring 15x10cm at its main axes, firmly attached to the parietal pericardium (fig. 2), in which a small area of rupture with the shape of a fissure (3cm long) was observed. Upon observation of the slices, the structure was found to be cystic, its wall 3mm thick, with a whitish granular internal surface and focal areas of thickening covered by a grayish friable material. At the internal surface, close to the posterior wall of the left ventricle, there was a round opening with regular borders, averaging 10x12cm in diameter that opened directly to the left ventricular cavity, close to the insertion site of the posterior papillary muscle (fig. 3). On the transversal slices of the ventricles, a healed myocardial infarction was observed with severe thinning of the ventricular wall that was down to 8mm in thickness. On this wall, in an area close to the opening to the ventricle and the saccular structure, we observed a round structure formed by gray tissue, firm to the touch, with a small 8x3mm opening (fig. 2). There were no other macroscopical changes in the rest of the endocardial surface of the left ventricle or of the other cardiac chambers. At the epicardial surface, besides the saccular formation and the adhesions described above, there were two areas of right coronary artery dilation: the largest, 20mm in diameter, was located in the 2nd and 3rd cm of the artery; the smallest, 15mm in diameter, was at the 7th cm of the artery (fig. 4). The transversal slices of the arteries at the site of the dilations disclosed severe thinning of the arterial wall, with 1mm at the thinnest point; arterial lumen at the site was totally obstructed by organizing thrombi. Recent thrombi caused partial obstruction also of the posterior interventricular and right marginal branches of the coronary artery. There were no other aneurysms or luminal thrombosis in the left coronary artery. No cavitory thrombi or other cardiac changes were observed.

Dissecting the aorta and its branches, a right femoral artery aneurysm, measuring 30 mm in diameter and with surgical stitches at its wall was present. The observation of the slices disclosed significant thinning of the wall with a minimal thickness of 2mm; the lumen was totally occluded by an organizing thrombus. The other arteries did not have other remarkable changes.

With the exception of liver congestion and cerebral petechia, there were no other macroscopic changes in other organs.

At microscopy, a necrotizing vasculitis in focal segments of the right coronary artery was observed, characterized by fibrinoid necrosis of the intima and media of the arterial wall, surrounded by an inflammatory infiltrate. In other areas, there was organization and scarring of the lesions, characterized by the presence of granulation tissue, endothelial proliferation and evanescence of the

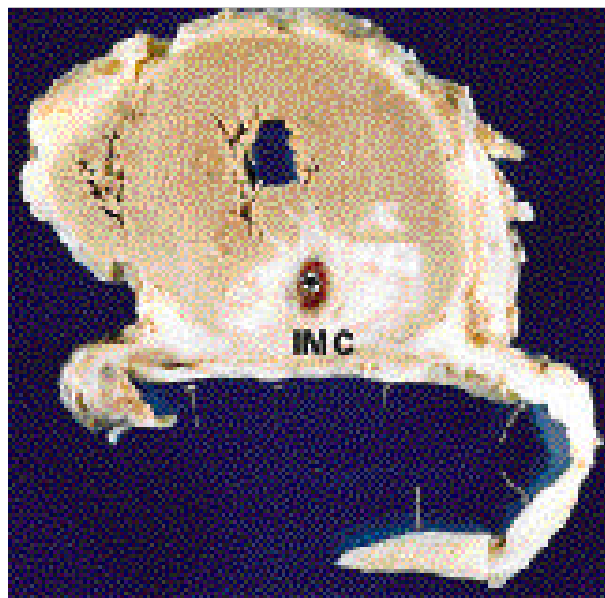


Fig. 2 - Transversal slice of the heart showing a healed myocardial infarction in the posterior wall of the left ventricle (IMC), there is a central area containing fibrinous material under organization (H). Firmly attached to it, the wall of the pseudoaneurysm is depicted (arrows).

media by the destruction of the elastic fibers and the internal elastic lamina (fig 5) but also areas with aneurysms and luminal thrombosis. Similar histological changes were observed in the right femoral artery. Besides the myocardial scar observed at the posterior wall of the left ventricle, the microscopic examination of the round structure described above suggested that it could be a coronary aneurysm filled with organized and recanalized thrombosis, with no signs of acute inflammation. There were minor changes of the renal arteries, such as elastic fiber rupture and medial fibrosis with endothelial proliferation. There were no other significant histological changes in other arteries of the systemic or pulmonary circulation.

In the kidneys, there was focal glomerular hyalinization. In the lungs, there was bronchiolitis and emphysema. In the liver, there were chronic passive congestion and centrilobular hepatic necrosis.

(Dr. Léa Maria M. Ferreira Demarchi)

Pathological diagnoses - 1) Bloody pericardial effusion, 2) ruptured saccular aneurysm of the left ventricular posterior wall, 3) Polyarteritis nodosa.

Comments

This is a case of a necrotizing vasculitis, affecting the coronary, renal and femoral arteries, without involvement of the pulmonary circulation or of the veins. The lesions were focal, and were in different evolutionary stages, from the fibrinoid necrosis of the arterial wall with inflammatory infiltrate, destruction of the media and internal elastic lamina and granulation tissue to scarring and the formation of aneurysms.

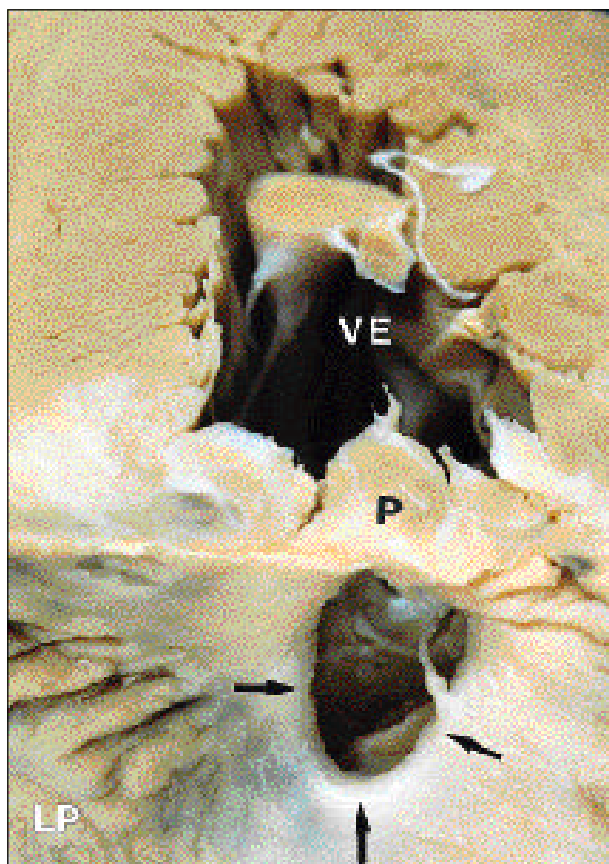


Fig. 3 - Oblique view of a transversal slice at the basal portion of the heart, showing severe thinning of the posterior wall (P). Note an orifice (arrows) linking the left ventricle (VE) to the lumen of the pseudoaneurysm (LP).

Considering the pathological changes observed and the main groups of necrotizing vasculitis, the best diagnosis for the present case would be polyarteritis nodosa^{19,20}.

Typically, polyarteritis nodosa is a necrotizing vasculitis that affects muscular arteries of medium and small size, sparing pulmonary arteries, arterioles and veins¹⁹⁻²². The mean patient age is 45 (ranging from 10 to 80) years^{10,19,23}. It affects more men than women at a ratio of 2 to 1^{14,19,24}. The vascular lesions are focal, occurring primarily at branching and bifurcation sites^{21,22}.

The lesions are thought to be mediated by immune complex deposition at the arterial wall, which would cause increased vascular permeability, complement activation and increased attraction of neutrophils to the involved areas^{25,26}. In some cases, polyarteritis nodosa is the result of hepatitis B infection, in which there is evidence of immune complex deposition triggered by viral antigens¹¹. There are reports showing that 30% of the polyarteritis nodosa patients have positive serologic evidence for the hepatitis B virus^{9,27}. Polyarteritis nodosa can be observed in association with other autoimmune diseases, such as SLE and rheumatoid arthritis^{7,28}.

At histology, four evolutive phases of the lesions can be identified²⁹⁻³¹: 1st) degenerative, characterized by

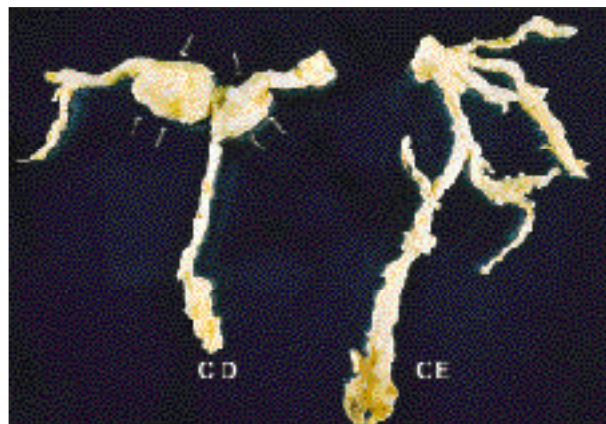


Fig. 4 - The dissection of the right (CD) and left (CE) coronary arteries is shown. Note the two aneurysms (arrows) in the right coronary artery.

fibrinoid necrosis of the intima and media; 2nd) of acute inflammation, characterized by the presence of the neutrophilic infiltrate in areas of fibrinoid necrosis; 3rd) with granulation tissue, which characterizes the beginning of the organization of the cited lesions; and 4th) of scarring, characterized by the replacement of the damaged areas by collagen.

The destruction of the media and of the internal elastic lamina favors the formation of aneurysms²⁹⁻³¹. All vascular lesions cited above promote thrombus formation, frequently resulting in the development of infarcts in the organs supplied by affected arteries²⁹⁻³³.

In a given patient, lesions of different phases can be observed simultaneously, which suggests that the vascular aggression by autoimmune complex deposition is either continuous or persistent in these patients²⁹⁻³³.

The kidney is the most frequently affected organ³⁴. Cardiac involvement was reported in 1/3 of the living patients and in 2/3 of the necropsy cases³²⁻³⁵.

The most frequent cardiac disturbances are vas-



Fig. 5 - Histological transversal slice of the first segment of the aneurysm of the right coronary artery, showing scar areas where there is replacement of all layers of the arterial wall by fibrosis (F), with evanescence of the elastic fibers and of the internal elastic lamina (arrows). In the vascular lumen a recent occlusive thrombosis (TRO) is observed. Movat stain, original magnification x10.

culitis³⁰⁻³², coronary thrombosis and aneurysms, pericarditis³² and the involvement of the electrical activation of the heart^{36,37}.

In the case discussed above, the involvement of the right coronary artery resulted in left ventricular posterior

wall infarction and, after healing, the formation of a saccular aneurysm. Its rupture resulted in the development of bloody pericardial effusion and death.

(Dr. Léa Maria M. Ferreira Demarchi)

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