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Aneurysms of the Coronary Arteries in Infants and Children

A Review, and Report of Six Cases

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Summary. In recent years large numbers of the so-called "mucocutaneous lymph node syndrome" or "Kawasaki's disease" have been described by Japanese workers, but instances of this disorder are only now being reported as isolated cases by European or North American physicians. The disease has, therefore, been considered to be a new entity. One of its most striking features is the development of aneurysms of the coronary arteries in infants or children, which may lead to sudden death. Aneurysms of the coronary arteries in childhood are rare, and hence it was considered relevant to report six such cases, and to examine their possible relationship to Kawasaki's disease. The pathological changes underlying the latter disorder are not well known; they are considered to be indistinguishable from infantile polyarteritis nodosa. A diagnosis of polyarteritis nodosa was also thought to be most likely to apply in the cases presented here, particularly in view of the frequency with which aneurysms of the coronary arteries have been found in this disorder. In the absence of valid pathological distinctions between Kawasaki's disease and infantile polyarteritis nodosa, the question arises whether these entities are, in fact, different, and whether Kawasaki's disease is the new entity it is assumed to be.

Key words: Coronary artery aneurysms – Mucocutaneous lymph node syndrome – Kawasaki's disease – Infantile polyarteritis nodosa.

Introduction

In recent years an interesting pediatric disorder has been described to which the name "mucocutaneous lymph node syndrome" (MCLNS) or "Kawasaki disease" has been applied (Editorial, 1976). It is characterized by fever not responding to antibiotics, a transient maculo-papular, non-vesiculating skin rash followed by desquamation of the skin of fingertips, conjunctival and oral muco-

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sal manifestations, swelling of cervical lymph nodes, cardiovascular signs, leukocytosis, positive C-reactive protein and raised erythrocyte sedimentation rate, proteinuria, and occasional signs and symptoms pointing to involvement of the joints, liver, or central nervous system (Kawasaki et al., 1974; Yanagisawa et al., 1974; Kato et al., 1975; Brown et al., 1976). The incidence appears to be highest in 1-year-olds, and a large proportion of the cases reported so far have been in children below the age of four years (Editorial, 1976). But whereas Japanese workers have by now described some 7000 instances of this disease (Kato et al., 1975; Brown et al., 1976), it seems that it is only now being recognized outside Japan, with a few cases reported here and there (Melish et al., 1974; Valaes, 1975; Wentworth and Silver, 1976; Brown et al., 1976; Radford et al., 1976; Lauer et al., 1976; John et al., 1976; Robinson and Adler, 1976). This has led to the suggestion that the disease is new (Kawasaki et al., 1974; Kato et al., 1975) – at least in Japan where, for reasons unknown, the incidence is unusually high. Since the etiology of the disease is not clear, the pathogenesis uncertain, and the published pathological findings scanty, it is difficult to comment on this suggestion with any degree of certainty. Of interest to the pathologist, however, is that in a high proportion of instances of this disease cardiovascular changes have been observed clinically, and that about 1–2% of these cases have died suddenly. This fatal potential of the disease has been recognized only comparatively late. In fact until 1972 it was thought to be a rather benign disorder (Tanaka et al., 1976). At necropsy of the fatal cases of Kawasaki's disease single or multiple aneurysms of the coronary arteries were found (Tanaka et al., 1976). Until now aneurysms of the coronary arteries in infancy and childhood have been thought to be sufficiently rare to warrant the publication of even single case reports (Malet and Evans, 1887; Clarke, 1896; Wilmer, 1945; Adelson, 1951; Bohman, 1954; Liban et al., 1954; Henry et al., 1960; Weller and Newstead, 1962; Bertelsen and Lindahl, 1964; Chamberlain and Perry, 1971; Götz, 1972; Liddicoat et al., 1974; Kühner et al., 1974; Holt and Jackson, 1975). Their etiology, however, is not always clear. It was, therefore, considered of interest to report the necropsy findings in 6 cases of coronary aneurysms occurring in young children, and to examine their possible relationship to the seemingly new "mucocutaneous lymph node syndrome".

Case 1

Clinical History

An 11-weeks-old boy with normal neonatal development was admitted to hospital with fever ranging up to 40.0°C, symptoms and signs of an acute left-sided otitis media, and enlargement of cervical lymph nodes. On the third day of illness a resistent maculo-papular rash appeared which varied in extent and intensity. The raised temperature also persisted for three weeks despite treatment with antibiotics. About that time a new feature appeared in the form of systolic and diastolic cardiac murmurs, moderate enlargement of the heart, ECG evidence of myocardial damage, and enlargement of liver and spleen. A week later necrosis of the distal phalanx of the fourth finger of the right hand developed. Simultaneously signs and symptoms attributed to a subdural hematoma were observed. The skull was explored and an old subdural hematoma was indeed found, but the child developed shock and died twelve hours after operation at the age of $17^1/_2$ weeks.

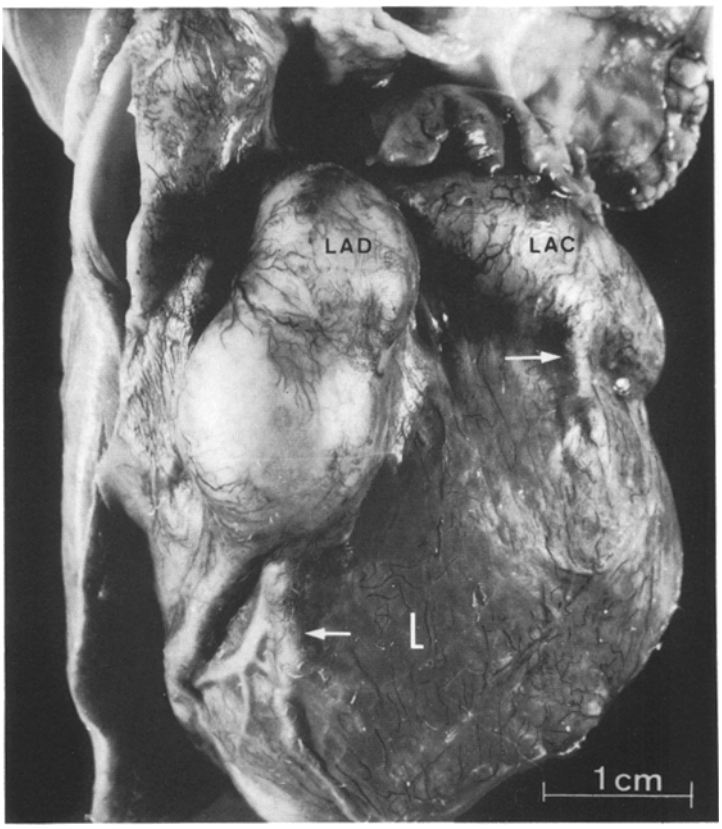

Fig. 1. Case 1: Gross appearance of the heart. – Note the large prominent aneurysm of the left anterior descending coronary branch (LAD) measuring 2.5 × 1.3 cm, and another fusiform aneurysm of the left anterior circumflex branch (LAC). The arrows point to the prominent and tortuous branches of the coronary arteries below the aneurysms

Laboratory Findings

The peripheral blood showed anemia (Hemoglobin: 8.1 g%), persistent leukocytosis ranging from 25,000 to 82,000 cells/cmm, and persistent marked thrombocytosis. The erythrocyte sedimentation rate (Westergren) was increased to 110 mm/h. There was also an increase of the alpha$_2$- and the gamma-globulins. Two weeks after the onset of the disease immunoglobulins IgA (220 mg/100 ml) IgG (1560 mg/100 ml) and IgM (270 mg/100 ml) were significantly increased, as were the transaminases, the creatine phosphokinase, and the gamma glutamyltranspeptidase. Serum electrolytes, blood urea, and creatinine levels were normal. Bacteriological investigations of stools, urine, and cerebrospinal fluid, and cultures of eyes and pharynx did not yield relevant findings. Staph. albus and Streptococcus viridans were grown in cultures from the nose in the fifth week of illness. The initial tentative working diagnosis had been sepsis with myocardial involvement, but the diagnosis of sepsis could not be verified bacteriologically.

Necropsy Findings

Gross Examination. The only relevant pathological changes were seen in the cardiovascular system. The body was that of a well developed male infant

Fig. 2. Case 1: Photomicrograph to show the wall of the proximal part of the coronary aneurysm (*LAD*) of Figure 1. It consists mainly of proliferated intima (*I*) which includes areas of incorporated thrombotic material (*th*). At the bottom remnants of the coronary media (*M*) are seen. (*T*) thrombus adhering to aneurysmal wall. H & E, ×120

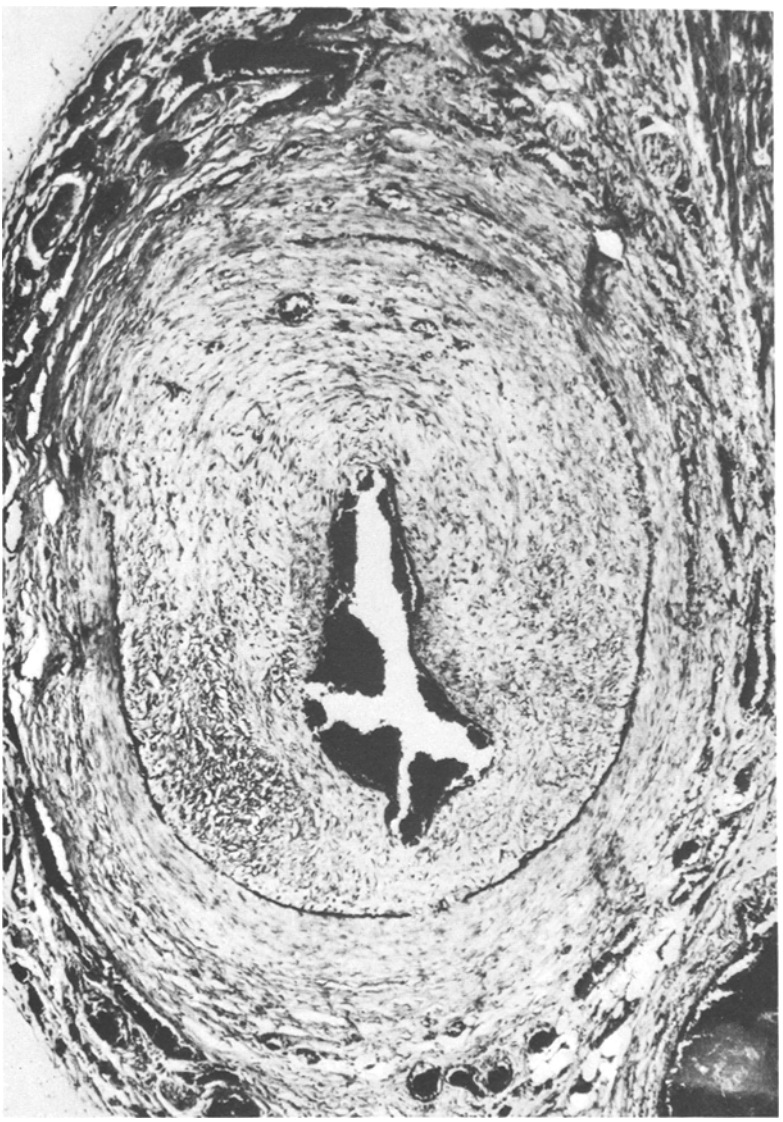

Fig. 3. Case 1: Photomicrograph of section through the left anterior descending branch of the coronary artery (LAC of Fig. 1) below the aneurysm, to show the narrowing of the arterial lumen by the proliferating intima. H & E, ×120

measuring 66 cm (crown-heel) and weighing 5800 g, showing enlargement of the heart (Wt. 41 g – Normal: 27 g). The proximal portions of the left anterior descending branch, of the left anterior circumflex branch and of the right coronary artery presented large, oval aneurysms which protruded markedly above the surface of the heart (Fig. 1). The aneurysms were filled with dark red, partly laminated thrombi. Below the aneurysms the arteries were thickened and tortuous (Fig. 1). The coronary ostia were free and the heart valves were normal. Several small fusiform dilatations were seen along both internal thoracic arteries. The walls of both carotid arteries were considerably thickened, particularly

at the bifurcations, and the lumen there was narrowed. The arteries of the right arm and hand with the gangrenous finger could not be examined. No changes were seen in any of the other arteries studied, including the renal or mesenteric vessels.

Microscopic Findings. The wall of the aneurysms of the coronary arteries consisted mainly of dense fibrous tissue, but in some areas, particularly underneath the thrombi, typical granulation tissue was seen containing capillaries, fibroblasts and moderate accumulations of lymphocytes. Proximally the aneurysms still presented fragments of the original media and were lined by a distinctly thickened intima (Fig. 2). Only small foci of frank necrosis were seen in these remnants of the arterial wall, but no inflammatory cell infiltrates were present. No fibrinoid lesions could be seen in any segment of the coronary or other arteries. The lumen of the coronary arteries below the aneurysmal dilatations was considerably narrowed by a proliferating, moderately cellular intima rich in ground substance (Fig. 3). A similar intimal proliferation was also found in both carotid sinuses and in the proximal part of both external carotid arteries, as well as in the internal thoracic arteries. No microscopic lesions were seen in any other arterial vessels.

Neither the initial nor the post-operative changes found in the skull were considered pertinent. Death was attributed to coronary insufficiency.

Case 2

Clinical History

A four months old male white child was admitted to hospital in a state of cardiovascular collapse. He had been born prematurely at 7 months gestational age by Caesarian section, but had been well until about 3 weeks prior to admission, when he developed what appeared to be an upper respiratory infection and discharging eyes. The infection cleared, but about 3–4 days before admission he was noted to be very pale, did not take his feeds too well and began to vomit. He rapidly became worse and was admitted with a temperature of 38°C, respiratory distress, pallor, cyanosis of lips, a marked tachycardia, barely palpable pulses, a muffled apical systolic Grade II murmur, rales in the chest and enlargement of the liver.

Laboratory Findings

Hemoglobin: 5 g%, Na: 139 mEq/L, CSF: No significant findings. Culture of nose and throat: No pathogens isolated. X-rays: Marked enlargement of the heart in the transverse diameter with an increased pulmonary vascular pattern suggesting congestive heart failure.

The patient was digitalized, given oxygen and packed cells, and seemed at first to respond to this treatment, but died suddenly, a few hours after admission. The tentative diagnosis was "acute myocarditis".

Necropsy Findings

Gross Examination. Apart from a moderate amount of fluid in the pleural, pericardial, and peritoneal cavities, and marked congestion of all organs, particularly pronounced in the brain, the pathological findings were limited to the

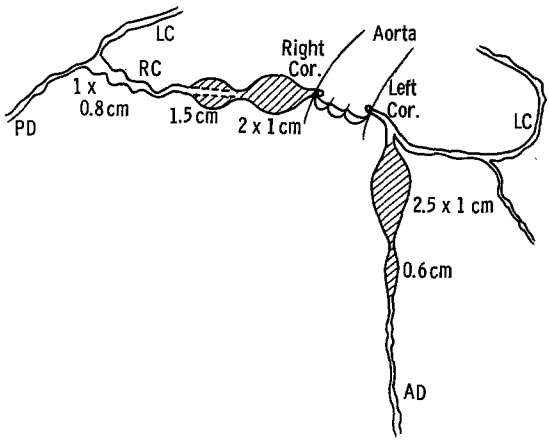

Fig. 4. Case 2: Schematic presentation of location and size of multiple coronary aneurysms found at necropsy. The obliquely shaded areas indicate the presence of thrombi in the aneurysms of the dilated and tortuous coronary arteries

heart which was considerably enlarged (Wt. 67 g – Normal: 27 g). All the branches of the coronary arteries appeared not only unduly prominent, but also markedly tortuous. Moreover, they presented several large, rounded or fusiform aneurysms of variable size (Figs. 4, 5), the largest measuring 2.5×1.0 cm, externally. On incision they were seen to be filled by thrombi, some of which were reddish and friable, whereas others contained paler, firmer and, in areas, adherent material. No calcification could be felt in any of the vessels or aneurysms. On cutting into the myocardium a large part of the left ventricle was distinctly yellow and soft, particularly towards the apex, but ill-defined patchy areas of similar appearance were also found in the midportion and towards the base of the heart. The cardiac valves and the coronary ostia appeared normal; no gross changes were seen in any of the other vessels studied.

Microscopic Findings. Multiple sections of the coronary vessels were taken from the aneurysmal dilatations as well as from the seemingly uninvolved segments. The latter showed no significant changes such as inflammatory cells, calcification, fibrinoid necrosis or destruction of the vascular wall. In the aneurysms, however, the wall appeared to consist largely of fibrous tissue with only scanty smooth muscle fibers and a few scattered remnants of elastic tissue (Fig. 6). The loss of elastic fibers was striking. No inflammatory cells were seen, and only a few pigmented macrophages were present in, and adjacent to, the thrombi. The thrombi themselves appeared to be rather recent in some areas, but in others obvious organization by granulation tissue and even recanalization had taken place. The granulation tissue showed a moderate infiltration by lymphocytes and mononuclear cells, but this was very patchy. The myocardium showed extensive loss of muscle mass with eosinophilic necrosis, disappearance of fibrils, and a scanty mononuclear response. Adjacent muscle fibers showed distinct non-lipid vacuolization. There was no evidence of myocarditis or valvular disease. It should furthermore be pointed out that other, non-cardiac, vessels appeared histologically normal.

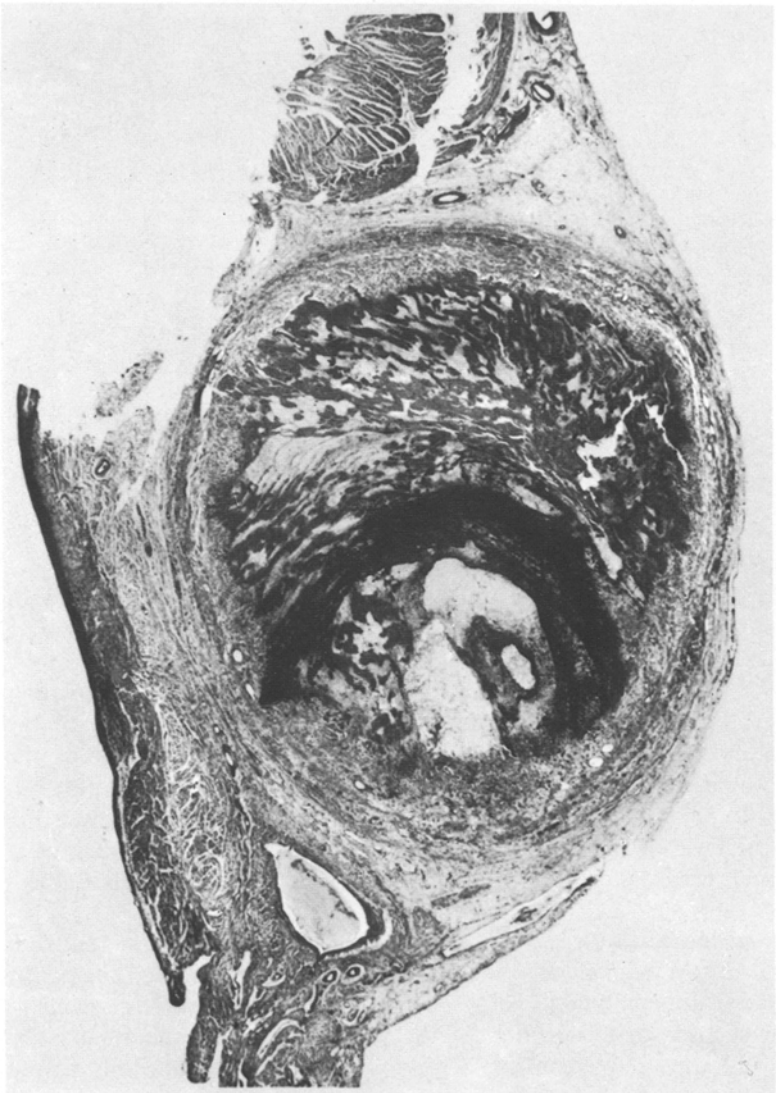

Fig. 5. Case 2: Low-power magnification of one of the aneurysms of Case 2 to show the laminated thrombus completely filling the lumen of the dilated vessel. H & E, ×9

Case 3

Clinical History

A five months old boy was well until four days before admission to hospital, when he developed a fever up to 40°C which did not respond to Penicillin. He had mild nasopharyngitis and bilateral otitis media, but on myringotomy no exudate was released. The child remained severely ill, with protean manifestations of an undiagnosed disease. He was febrile and anemic, requiring four blood transfusions. There developed a right facial palsy and a diffuse macular rash over the trunk and extremities, which spared the soles and palms; it was thought to be due to drug sensitivity. The child had a marked leukemoid reaction up to 61,000 WBC/cmm, with 75% neutrophils and 3% eosinophils. Bacteriological investigations were consistently negative. Shortly before his death 24 days after admission a pericardial friction rub was noted, with a heart rate of 150–170 beats/min,

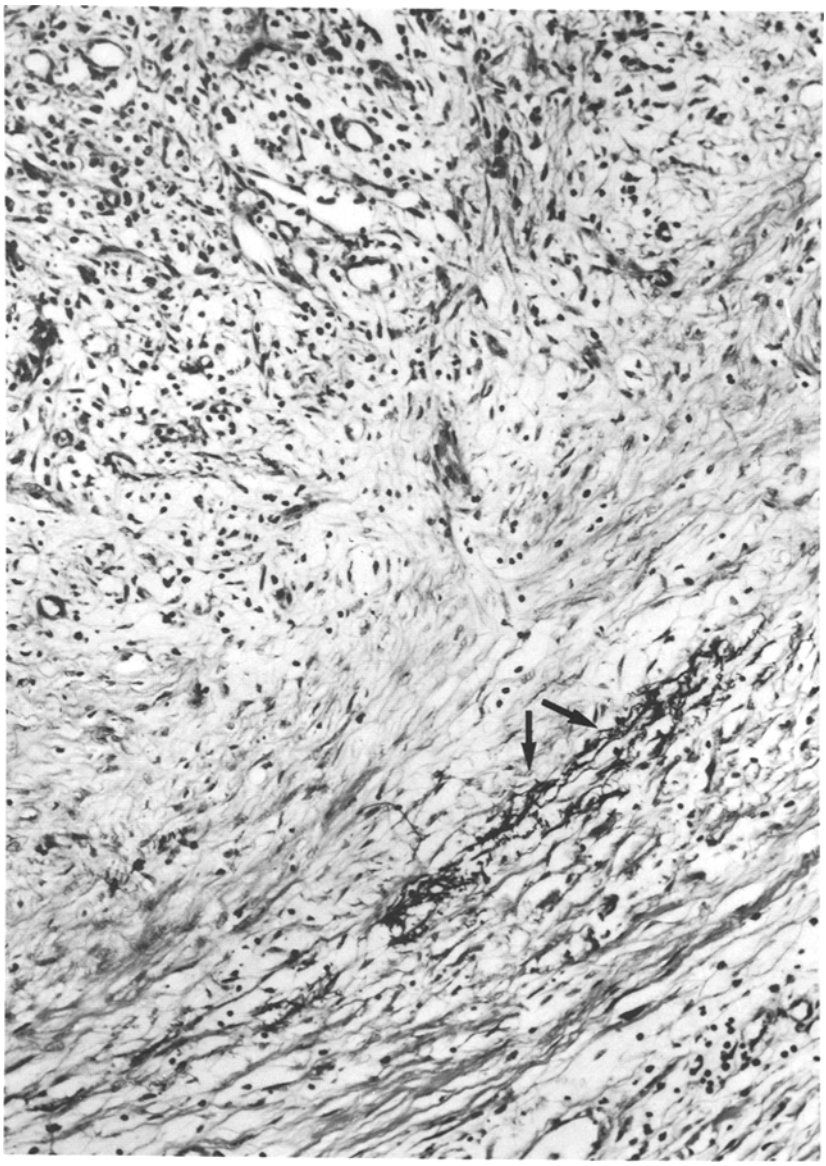

Fig. 6. Case 2: Photomicrograph to show the residual elastic shreds (arrows) in the wall of the aneurysm of the coronary artery with organizing thrombus and granulation tissue formation. Weigert's elastic stain, × 150

a Grade II systolic murmur and gallop at the apex. Blood pressure recorded for the first time was 160/100 mm Hg. X-rays showed enlargement of the heart suggestive of pericarditis.

Necropsy Findings

The heart showed aneurysmal dilatation of all proximal segments of the coronary arteries with thinning and destruction of the media. The affected arterial segments showed an infiltration mainly by lymphocytes and histiocytes, with an admixture of neutrophils, marked periarteritis, and focal fibrinoid changes. Proliferating fibroblasts with a loose collagen network were also present in many

areas. The lumen of the arteries contained organizing thrombus. In the pericardial sac there was a thick fibrinous, but sterile, exudate. An arteritis similar to, but not as severe as that seen in the coronaries, was found in the renal arteries, and in some of the branches of the hepatic, peritesticular and mesenteric arteries. No gross or histological lesions were present in the spleen, lungs, pancreas, adrenals, brain, or skin. The kidneys, however, showed recent infarcts as well as an old fibrotic scar.

Case 4

Clinical History

A 5-months-old boy was well until the age of 3 months when he had an upper respiratory infection which did not respond to treatment with Penicillin. His fever persisted and he developed a rash. On admission to hospital he was markedly anemic (Hgb: 4.8 g%). His peripheral blood showed 23% reticulocytes and a WBC of 67,000 cells/cmm with 78% neutrophils. Intensive investigations failed to show the cause of the anemia and of the leukemoid reaction. After 3 weeks in hospital the child went into intermittent congestive heart failure. ECG disclosed a low voltage and left ventricular hypertrophy. His remaining hospital course of 4 weeks was punctuated by episodes of metabolic acidosis, electrolyte imbalance, albuminuria, repeated episodes of increasing cardiac failure, paralytic ileus, uremia and finally a complete renal "shut-down".

Necropsy Findings

Autopsy disclosed an enlarged, but normally formed, heart with a hypertrophied left ventricle (Wt. 80 g – Normal: 29 g). There was a large aneurysm of the right coronary artery which on microscopic examination had severe intimal fibrous thickening with a generally well maintained media and internal elastica. There was in addition extensive thrombosis with recanalization. The lack of any inflammatory response within, or surrounding, the vessel wall was notable. Small foci of fibrosis were present in the myocardium. Obliterative changes without inflammation were also seen in the renal arteries, and a recent infarct was present in the right kidney.

Case 5

Clinical History

A 2-year-old girl had been entirely well until 2 weeks prior to admission when she began to be irritable and anorexic. Nine days later she became febrile and had cervical lymphadenopathy for which she was treated with Penicillin. Three days prior to admission she developed a morbilliform rash which became generalized and faded when Penicillin was replaced by Achromycin. Suddenly, however, she became critically ill and was admitted to hospital. On admission the child was found to be acutely ill, febrile and pale. She had a peripheral maculo-papular rash and erythema of palms and soles. It was thought that her rash was due to hypersensitivity to Penicillin. Her throat was injected, but the lungs were clear. The heart sounds were rapid and muffled. X-rays showed the cardiac silhouette to be enlarged and prominent bronchovascular markings suggested heart failure. The ECG was normal. Hgb: 12.0 g%, WBC: 52,000 decreasing to 14,000 with 48% neutrophils, 44% lymphs, 7% monos, 1% baso. ESR: 36 mm/h. No infectious etiology of the illness could be determined. Despite treatment the child died with cardiac arrest 16 days after admission.

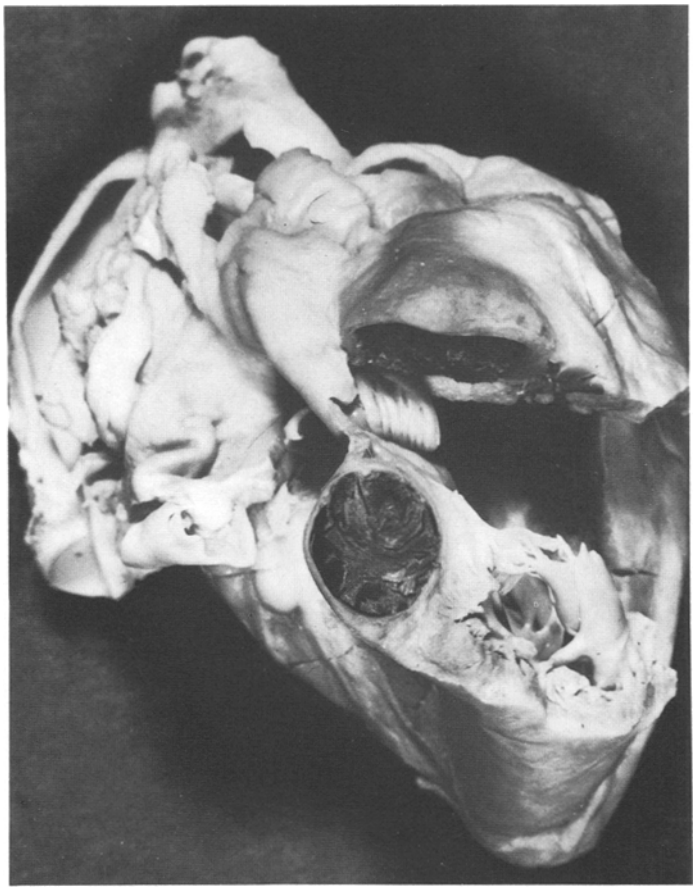

Fig. 7. Case 5: Gross appearance of the heart. – Note the recent thrombus in the large aneurysm of the right coronary artery

Necropsy Findings

Significant autopsy findings were limited to the heart. The pericardial sac was distended with 200 ml of light yellow fluid which contained abundant fibrin. The configuration of the heart was normal, but the left coronary artery and the proximal one-half of its anterior descending branch were aneurysmally dilated and thrombosed (Fig. 7). Similar changes were present in the main proximal portions of the right coronary artery. The left circumflex branch was spared. Microscopic examination of the aneurysms disclosed focal thinning and necrosis of the arterial wall. There was focal acute vasculitis, but elsewhere the inflammation appeared more chronic in nature and was characterized by destruction of the media and its replacement by proliferating young connective tissue. A fresh thrombus was present in the lumen of the aneurysm. The myocardium showed focal eosinophilia of muscle fibers and a few areas of frank necrosis

with neutrophils. The remainder of the vascular system was normal. Death was attributed to occlusion of the coronary artery.

Case 6

Clinical History

A 3-year-old white boy was well until 3 weeks prior to his first admission when he complained of a febrile upper respiratory infection which did not improve with antibiotics. He had a transient rash, viewed as a response to Penicillin. Physical examination on admission showed oral Candidiasis only. However, laboratory studies disclosed a sedimentation rate of 110 mm/h and a microcytic hypochromic anemia (Hgb: 8.9 g%). During his stay in hospital he had a transient Yersinia gastroenteritis and developed joint pains. His hands, ankles and feet became swollen and hot, and his fingers appeared fusiform. Tests for rheumatoid arthritis remained negative, but he responded to treatment with aspirin. He continued to do well at home, but was readmitted one month later with another febrile upper respiratory tract infection leading to pneumonia complicated by pneumothorax. The persistent anemia required treatment by transfusion, but the child was quite well when discharged again. At that time the sedimentation rate was 29 mm/h and the WBC: 9200 cells/cmm with a normal differential count.

Four months later he was readmitted. He was acutely ill with grunting respirations, bronchial breathing over the right side of the chest, and rales and rhonchi over the left side. Heart and liver were enlarged, and the ECG showed low voltage ST-T segment changes. He was treated with digitalis, steroids and ampicillin, but 12 h after admission he complained of severe chest pain and sustained a fatal cardiac arrest.

Necropsy Findings

The significant findings were limited to the cardiovascular system. The heart weighed 75 g (Normal for age: 61 g) and was grossly not remarkable except for dilatation of both ventricles and of the right atrium. The proximal portions of the left anterior descending coronary artery and the left anterior circumflex branch, however, showed aneurysmal dilatations. The wall of the aneurysms consisted of fibrous tissue, and the lumen was occluded by organized or fresh thrombi. In the less dilated segments of the coronary arteries a marked intimal thickening and severe hyalinization of the media was present, with focal revascularization of the media and rare linear calcium deposits. In the more distal coronary segments mainly the intima was affected. It showed a severe uniform thickening with subsequent marked narrowing of the lumen. The myocardium, particularly of the interventricular septum and of the left ventricle, was markedly scarred. In addition there was present extensive acute myocardial infarction with coagulation necrosis and demarcation by neutrophils.

Most of the other muscular arteries examined, with the notable exception of the pulmonary and cerebral vessels, but including the intercostals, the carotids, and the renal arteries, showed severe intimal fibrous scarring, splitting of the internal elastica, and focal scarring of the media with occasional calcification. No histological evidence of an acute or chronic vasculitis was seen, and no fibrinoid necrosis was present. In the iliac arteries recanalized thrombi were found. There was no infarction in any organ other than the heart. The abdominal

aorta grossly was a rigid vessel with a nodular intimal surface. Microscopic sections showed severe fibrous scarring of the intima and media with focal calcium deposition deep in the media.

Discussion

Until recently aneurysms of the coronary arteries had been seen only by pathologists at necropsy. With the refinement of modern diagnostic procedures such aneurysms have now also been demonstrated in adults and in children during life (Sherkat et al., 1967; Cafferky et al., 1969; Chamberlain and Perry, 1971; Liddicoat et al., 1974; Kato et al., 1975; Radford et al., 1976) and have even been operated upon (Wright et al., 1971; Ghahramani et al., 1972; Dawson and Ellison, 1972; Seabra-Gomes et al., 1974). With the help of coronary angiography Kato et al. (1975) recently found that 12 out of 20 patients with the MCLNS had abnormal angiograms. Seven of these had aneurysms of the coronary arteries, but in two patients complete regression of established coronary aneurysms appears to have been demonstrated by consecutive vascular studies. It, therefore, appears probable that aneurysms of the coronary arteries will cease to be the pathological curiosities which until now they had been thought to be, so that pathologists as well as clinicians should become thoroughly familiar with this phenomenon.

There have in the past appeared several surveys and classifications of aneurysmal dilatations of the coronary arteries (Packard and Wechsler, 1929; Scott, 1948; Crocker et al., 1957; Munro-Faure, 1959; Roberts and Fetterman, 1963). One might have hoped that these efforts would lead to a better understanding of this phenomenon, but there is still considerable uncertainty concerning its etiology and pathogenesis. The early classification of aneurysms as "atherosclerotic" and "mycotic-embolic" (Packard and Wechsler, 1929) was amplified by Scott (1948) who introduced the third, and largest, category of "congenital" aneurysms, defined mainly by an absence of obvious contributory factors. Although he cautioned that "possibly it would be wiser to leave this whole group as unclassified until further evidence can be obtained ...", the concept of "congenital" aneurysms of the coronary arteries was readily accepted and is still being applied today (Cafferky et al., 1969; Rose, 1971; Ghahramani et al., 1972; Seabra-Gomes et al., 1974).

In 1959 Munro-Faure published an important review of 18 cases of necrotizing arteritis of the coronary vessels occurring in the first year of life. She was prompted to do so by a case of her own, an infant aged 4 months who died with thrombosis of aneurysmally dilated coronary arteries. Munro-Faure (1959) distinguished essentially two groups – cases with generalized arteritis and cases with predominant involvement of the coronary arteries. Transitional forms between the two groups did, however, occur. Perhaps more significant was Munro-Faure's (1959) observation that of the 19 cases reviewed 12 had not only similar gross findings at necropsy, consisting of single or multiple aneurysms of the coronary arteries, but that the clinical pictures of these cases also presented features which resembled each other. It is difficult to be certain at this stage

about some of the important traits of these clinical pictures, and unfortunately the same must be said about some of the clinical and laboratory features of the cases presented here, some of which are older instances from our files. It seems, however, that in both series there were present various combinations of signs and symptoms – fever not responding to treatment, ocular signs, ill-defined upper respiratory tract infections, skin rashes, swollen lymph nodes, cardiac involvement, leukocytosis, arthralgias and meningeal signs – that are now also listed as components of the clinical picture of Kawasaki's disease. One may, therefore, well raise the question whether at least some of these cases would not have been diagnosed today as instances of the "mucocutaneous lymph node syndrome".

A few years after Munro-Faure (1959) had published her survey, Roberts and Fetterman (1963) undertook another review of the reported instances of coronary artery disease in infants, and added two examples of their own. Like Munro-Faure (1959), Roberts and Fetterman (1963) pointed out that "a preliminary screening of the features of these 20 cases caused us to wonder whether a more or less constant pattern of clinical findings might not exist" in this disorder. The coronary arteries were predominantly affected in 18 out of these 20 cases, and in 11 of these they presented aneurysmal dilatation. Involvement of other vessels such as the renal or mesenteric arteries was also present in some of these cases. The histological and clinical features led Roberts and Fetterman (1963) to suggest that the underlying disease was infantile polyarteritis nodosa (IPN). The precise relationship between this disorder and the adult form of polyarteritis is still to be determined (Tanaka et al., 1976). That the heart is frequently involved in the adult form of this disease is well known (Roberts and Fetterman, 1963; Reimold et al., 1976) from the time when Kussmaul and Maier first described the "nodular thickening ... of the main branches of the coronary arteries of the heart ..." in 1866. The infantile form is characterized by an even higher incidence of changes in the coronary arteries (Roberts and Fetterman, 1963; Benyo and Perrin, 1968; Reimold et al., 1976). Roberts and Fetterman (1963) have pointed out that the true nature of the disease in the young child may, however, not always be recognized for two reasons. In the first place the fibrinoid change of the vessel walls, which tends to alert many pathologists to the possibility of polyarteritis, is not always a prominent feature in the coronary arteries of infants and younger children. This has also been reported by others (Krouse et al., 1974), and was likewise seen in some of the cases presented here. The other point to be made is that, as Roberts and Fetterman (1963) have put it, "... if the arterial involvement were to be largely or entirely limited to the coronary arteries, and the patient were to die with all affected arteries in the reparative stage, one might hesitate to make the diagnosis of polyarteritis nodosa". Although in IPN various developmental stages may be seen side by side (Benyo and Perrin, 1968), sometimes only the healing or healed stage may be present and, as in some of our cases, the inflammatory component may be entirely missing. The suggestion of Roberts and Fetterman (1963), that most of the aneurysms of the coronary arteries of the type described here are an expression of polyarteritis nodosa in infants has, so far, not been disproved.

There is another aspect of this suggestion which is pertinent here. It concerns

the relation of IPN to Kawasaki's disease, to which Fetterman and Hashida (1974) have recently drawn attention. Kawasaki et al. (1974) and Kato et al. (1975) stated that MCLNS "may be misdiagnosed as ... infantile periarteritis nodosa", and Kawasaki et al. (1974) maintained that "the clinical pattern of MCLNS is ... different from that of periarteritis nodosa in infancy, though description of the clinical features of the latter is insufficient in the literature". Kato et al. (1975), however, stated that "... a relationship between the two disorders [cannot] be excluded with certainty". This, as has already been pointed out, had also been our impression on comparing the clinical data of the cases presented here with the published reports of IPN and of the MCLNS. Radford et al. (1976) likewise thought that a "precise separation [of these entities] has not been accomplished". From the point of view of the pathologist such a distinction certainly cannot be maintained. It is significant that Tanaka et al. (1976), who have described the necrospsy findings in 29 Japanese cases of the MCLNS have concluded that "the resemblance between the arteritis observed in cases of MCLNS and polyarteritis or periarteritis nodosa appears to be more than incidental ...". Fetterman and Hashida (1974) were convinced that the structural alterations in the MCLNS were indeed indistinguishable from those of IPN. That was also the view of Melish et al. (1976), who had been the first to show that the MCLNS was not limited to Japan, and of Landing and Larsen (1975). Until such time, therefore, that etiological, epidemiological, immunological, and pathological studies conclusively demonstrate significant differences between Kawasaki's disease on the one hand, and infantile and adult polyarteritis nodosa on the other, we are inclined to agree with the suggestions of Fetterman and Hashida (1974), Beck (1976), and of Robinson and Adler (1976) that the mucocutaneous lymph node syndrome may not be altogether the new entity it is now assumed to be.

A number of questions remain unanswered. Why has the disease assumed the proportions reported from Japan, but is being recognized only now elsewhere? What importance, if any, should be attached to the reports of rickettsia-like bodies in material from patients with MCLNS? (Hamashima et al., 1973.) Above all, why are the coronary arteries so frequently and so severely, at times even exclusively, affected in the infantile form of polyarteritis nodosa and the MCLNS – diseases which are, potentially at least, generalized disorders? (Munro-Faure, 1969; Roberts and Fetterman, 1963; Benyo and Perrin, 1968; Reimold et al., 1976; Yanigasawa et al., 1974; Melish et al., 1976; Tanaka et al., 1976.) Conceivably this predilection for the coronary arteries is an expression of hemodynamic factors, indicating a higher functional load to which the growing coronary vessels may be exposed at certain stages of their development. A large number of cases with fatal aneurysms of the coronary arteries have been reported in children below the age of 1 year. At this age a profound remodelling and strengthening of the arterial wall is stated to occur in the proximal segments of the coronaries (Gross et al., 1934). Perhaps the accelerated growth may render these vessels more susceptible, and thus be responsible for the high incidence of aneurysms of the coronary arteries in the infantile form of polyarteritis, by comparison with other vascular territories. These suppositions need to be verified by more detailed studies, however.

One additional topic of interest emerges from these considerations. It has

already been pointed out that aneurysms of the coronary arteries are frequently considered to be "congenital" largely because no obvious etiological factors can be determined (Cafferky et al., 1969; Rose, 1971; Ghahramani et al., 1972; Seabra-Gomes et al., 1974). If we except the coronary aneurysms of the arteriovenous fistula type (Harris, 1937; Davison et al., 1955; Valdivia et al., 1957; Gould, 1960; Newcombe et al., 1964; Wright et al., 1971) or of the type described by Lovitt, Jr. and Lutz, Jr. (1974), the allegedly congenital nature of some of the other aneurysms must be questioned, the more so since angiographic studies of the MCLNS have now shown how frequently the coronary arteries are involved in this disorder. The studies of Kato et al. (1975) must be singled out in this context. These workers demonstrated not only that previously established aneurysms can apparently disappear, but also reported the very interesting case of an asymptomatic child who, two years after the disappearance of signs and symptoms of the MCLNS, was found still to have an aneurysm of the left coronary artery. One may well wonder whether this aneurysm would not have been considered "congenital", if the preceding history of the MCLNS had been misinterpreted or ignored, or had not been known at all. An equally striking case has been reported by Wentworth and Silver (1976). Here the interval between the initial disease and death was almost 6 years. It may, therefore, be justified to question the "congenital" nature of at least some of the aneurysms that have been reported under this heading, and to ask whether a preceding disorder of the type of polyarteritis nodosa or Kawasaki's disease has been, or can be, excluded.

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Note Added in Proof. A detailed description of the mucocutaneous lymph note syndrome, including one fatal case with aneurysms of the coronary arteries, is given by Melish, M.E., Hicks, R.M., Larsen, E.J.: Mucocutaneous lymph node syndrome in the United States. J. Amer. Med. Assoc. **130**, 599–607 (1976)